University of Alberta

Synthesis of a Versatile Precursor to Ruthenium-Diphosphine Complexes and Reusable ROMPgel Hydrogenation Catalysts

By

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Abstract

The complex *trans*-$RuCl_2(NBD)Py_2$ (**I**) was synthesized from the polymeric compound $[RuCl_2(NBD)]_n$ (**II**) in less than twenty hours by first preparing $RuCl_2(NBD)(Pip)_2$ (**III**), followed by reaction of **III** with excess pyridine. Compound **I** was examined as a starting material for the preparation of ruthenium-diphosphine complexes. Reaction of **I** with a large variety of diphosphine ligands gave the complexes *trans*-$RuCl_2$(diphosphine)py_2 (**IV**) { diphosphine = (*R*)-BINAP, (*R,R*)- or (*S,S*)-CHIRAPHOS, (*R*)-(*S*)-JOSIPHOS, (*R,R*)-Me-DUPHOS, (*R,R*)-NORPHOS, (*R,R*)- or (*S,S*)-SKEWPHOS)} or $[Ru_2Cl_3(diphosphine)_2Py_2]^+$ (**V**) (diphosphine = (*R,S,R,S*)-Me-PennPhos). The X-ray crystal structure of **V** is the first ever for a metal-PennPhos complex. Complexes **IV** were found to be catalyst precursors for asymmetric hydrogenation of a variety of olefins and functionalized ketones. Reaction of complexes **IV** with DPEN (either enantiomer) gave $RuCl_2$(diphosphine)(DPEN) complexes, that are useful as catalyst precursors for rapid and selective asymmetric hydrogenation of aryl-alkyl ketones.

The structure of the NORPHOS ligand renders it susceptible to ROMP reactions. The complex *trans*-$RuCl_2$((*R,R*)-NORPHOS)Py_2 (**VI**) was examined as a monomer in an attempt to prepare supported catalyst precursors via the ROMP protocol. It was found that ROMP of neat **VI**, using Grubbs' catalyst $RuCl_2(CHPh)(PCy_3)_2$ (**VII**) or $RuCl_2(CHPh)(IMesH_2)(PCy_3)$ (**VIII**), did not result in the formation of polymers because the initial insertion product of **VI** into **VII** or **VIII** was too crowded for a second monomer of **VI** to react. The polymerization was achieved in the presence of cyclooctene (COE), a less sterically demanding

spacer olefin. The polymer obtained by copolymerization of **VI** and COE using **VII** or **VIII** was converted into the DPEN analogue by reaction with (*R,R*)-DPEN at r.t. for two hours. The DPEN containing polymer was used for asymmetric hydrogenation of 1'-acetonaphthone giving 74 % ee (*S*) that is higher than the 51 % ee (*S*) obtained using the homogeneous catalyst $RuCl_2$((*R,R*)-NORPHOS)((*R,R*)-DPEN). The polymer was reused ten times in hydrogenation reactions without significant loss in activity or selectivity. This is the first time a ROMP polymer has been used in asymmetric hydrogenation.

To my mother

Janet Merab Akotsi

(1940-2001)

I fetched that which remained

Acknowledgement

I am greatly indebted to my Research Supervisor Dr. Steven H. Bergens for the excellent projects and guidance he offered during the course of this study. In particular, I am impressed by the fact that all the projects I worked on were new to the group and I had the privilege of doing the pioneering work. I wish to thank all the group members (past and present) for their lively discussions, intellectual discourses and jokes in the Laboratory. Although it is difficult to single out any particular group member for special mention, I sincerely appreciate the efforts and contribution of Rhonda Reid towards the contents of this dissertation and the kind hearted Dianxue Cao for keeping me in his tent on many a camping trip.

I greatly appreciate the efforts put in by the vastly experienced and talented people in the NMR Laboratory, Microanalysis Laboratory, Glassblowing Shop, Machine Shop and X-ray Structure Determination Laboratory. I owe special thanks to Drs. Bob MacDonald and Michael Ferguson of the Structure Determination Laboratory for the enthusiasm with which they did their work and without whom, a large section of this work would not have been possible. I also would like to give special thanks to Glen Bigam, Gerdy Aarts and Lai Kong of the NMR Laboratory for their devotion to duty and willingness to assist whenever called upon.

I could not have gone through this course without paying the tuition fees. In this regard, I wish to thank the Chemistry Department, University of Alberta for

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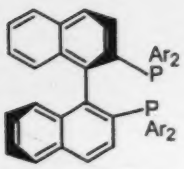
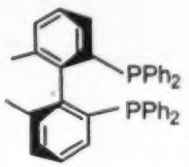
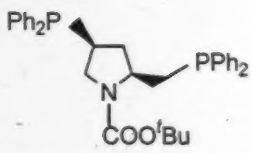
Structures of Some Chiral Diphosphines for Asymmetric Hydrogenation



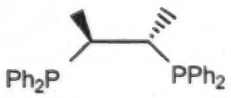
(*R*)-BINAP: Ar = C_6H_5
(*R*)-TolBINAP: Ar = 4-$CH_3C_6H_4$
(*R*)-XylBINAP: Ar = 3,5-$(CH_3)_2C_6H_3$



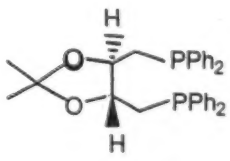
(*R*)-BIPHEMP



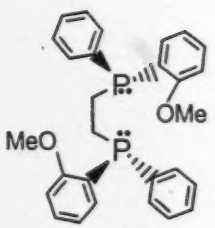
(*S,S*)-BPPM



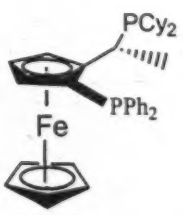
(*S,S*)-CHIRAPHOS



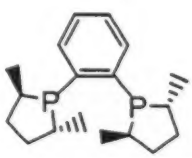
(*S,S*)-DIOP



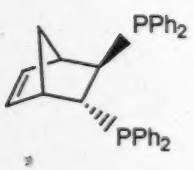
(*R,R*)-DIPAMP



(*R*)-(*S*)-JOSIPHOS

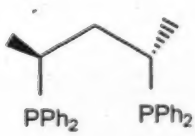


(*R,R*)-Me-DUPHOS



(*R,R*)-NORPHOS

(*R,S,R,S*)-Me-PennPhos



(*S,S*)-SKEWPHOS

List of Abbreviations and Symbols

acac	acetylacetonate
AIBN	2,2'-azobisisobutyronitrile
anal	analysis
Å	angstrom
atm	atmosphere(s)
av	average
β-Dex	*β*-cyclodextrin
BINAP	(*R*)- or (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BIPHEMP	(*R*)- or (*S*)-6,6'-dimethyl-2,2'-bis(diphenylphosphino)-1,1'-biphenyl
BPPM	(2*S*,4*S*)- or (2*R*,4*R*)-4-diphenylphosphino-2-diphenylphosphinomethyl-1-(N-*t*-butoxy)pyrrolidine
CHIRAPHOS	(2*S*,3*S*)- or (2*R*,3*R*)-2,3-bis(diphenylphosphino)butane
COD	*cis*-1, 5- cyclooctadiene
Cp	cyclopentadienyl
cydn	(1*R*,2*R*)-cyclohexyldiamine
DAIPEN	(*R*)- or (*S*)-1,1-di-4-anisyl-2-isopropyl-1,2-ethylenediamine
DCP	dicyclopentadiene
dcypb	1,4-bis(dicyclohexylphosphino)butane
DIC	diisopropylcarbodiimide

DIOP	(2*R*,3*R*)-or (2*S*,3*S*)-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPAMP	(*R*,*R*) or (*S*,*S*)-1,2-bis[(*o*-methoxyphenyl)-phenylphosphino]ethane
DMA	*N*,*N*′-dimethylacetamide
DMF	*N*,*N*′-dimethylformamide
DPEN	(*R*,*R*)- or (*S*,*S*)-1,2-diphenylethylenediamine
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
ee	enantiomeric excess
equiv	equivalents(s)
GC	gas chromatography
GTA	γ-cyclodextrin
h	hour(s)
HOBt	hydroxybenzotriazole
$IMesH_2$	1,3-dimestyl-4,5-dihydroimidazol-2-ylidene
JOSIPHOS	(*R*)-(-)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl] ethyldicyclohexylphosphine
MAA	methyl α-acetamidocinnamic acid
MAC	methyl α-acetamidocinnamate
Me-DUPHOS	1,2-bis((2*R*,5*R*)- or (2*S*,5*R*)-(2,5-dimethylphospholano) benzene

MeO-BINAP	(*R*)-or (*S*)-2,2'-bis(bis(*p*-methoxyphenyl)-phosphino)-1,1'-binapthyl
Me-PennPhos	*P,P'*-1,2-phenylenebis[(1*R*,2*S*,4*R*,5*S*)-2,5-dimethylphosphabicyclo[2.2.1]heptane]
min	minute(s)
mm	millimeter(s)
mmol	millimol(s)
mL	milliliter
NBD	norbornadiene
NMR	nuclear magnetic resonance
NORPHOS	(2*S*,3*S*)- or (2*R*,3*R*)-2,3-bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene
PCy_3	tricyclohexylphosphine
PDMS	poly(dimethylsiloxane)
PEG	polyethyleneglycol
PIGIPHOS	bis{(*S*)-1-[(*R*)-2(diphenylphosphino)ferrocenyl]ethyl}cyclohexylphosphine
Pip	Piperidine
PS-CH_2NH_2	amino polystyrene
psi	pounds per square inch
Py	pyridine
rac	racemic
ROMP	ring opening metathesis polymerization

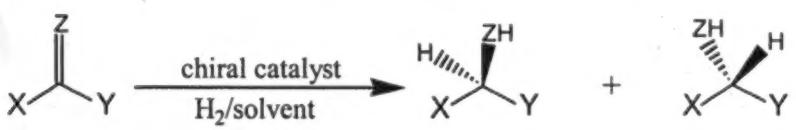
r.t.	room temperature
SKEWPHOS	(2*S*,4*S*)- or (2*R*,4*R*)-2,4-bis(diphenylphosphino)pentane
tmen	1,1,2,2-tetramethylethylenediamine
TON	turnover number
TOF	turnover frequency

Chapter 1

Introduction

Some general definitions. The term catalyst was coined by Berzelius in 1835 to refer to substances that increase the rate of chemical reactions without themselves being consumed.[1] This definition highlights two important features of the catalyst. First, the catalyst is not consumed during the reaction and less than stoichiometric amounts are often required. Thus in principle, it is possible to recover and reuse the catalyst at the end of the reaction. Second, the focus of catalysis, at least in the early stages of its development, was to accelerate the rate of the reaction. With time, more complex processes were developed and the emphasis on catalysis shifted towards improving the selectivity of these catalysts. One area where the selectivity of the catalyst determines its viability is in asymmetric hydrogenation.

Asymmetric hydrogenation refers to the preferential hydrogenation of a reactant containing prochiral faces into one enantiomer of the product over the other (equation 1-1). The goal in asymmetric hydrogenation is to obtain enantiopure products. The



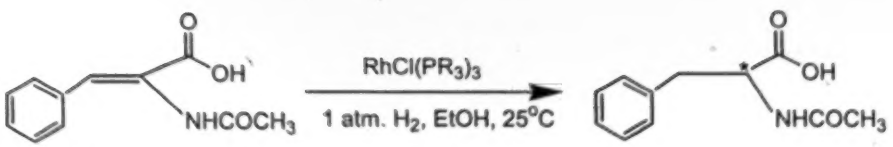
(1-1)

selectivity of the catalyst is expressed in terms of enantiomeric excess (ee) which is defined in equation 1-2.

$$ee\ \% = \frac{\text{major enantiomer - minor enantiomer}}{\text{major enantiomer + minor enantiomer}} \times 100 \qquad \textbf{(1-2)}$$

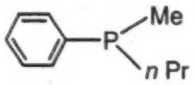
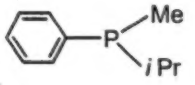
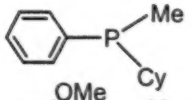
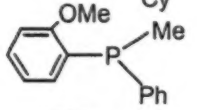
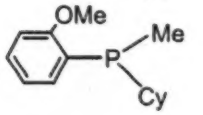
For the production of chiral molecules, at least one of the starting materials must be chiral. In the case of asymmetric hydrogenations the chiral reactant is often a transition metal complex. The catalyst reacts with a molecule of the prochiral substrate to produce a molecule of the product with a preference for one enantiomer over the other and then goes back to react with another molecule of the substrate. The completion of one catalytic cycle is called a turnover. The number of moles of product produced per mole of catalyst is known as the turnover number (TON). The number of moles of product produced per mole of catalyst per unit time is the turnover frequency (TOF). In theory, the catalyst can go through a number of catalytic cycles to produce a substantial amount of enantioenriched product. This process is referred to as chiral multiplication.

Diphosphine ligands as agents for chiral multiplication. Catalysts for asymmetric hydrogenation are often transition metal complexes having chiral phosphine ligands.[1,2] The development of catalysts for asymmetric hydrogenation began as the modification of the highly efficient Wilkinson's hydrogenation catalyst [$RhCl(PPh_3)_3$],[3] by replacing triphenylphosphine with chiral phosphines.[4,5] Knowles and co-workers believed that, in order to obtain high ee values, the asymmetry would have to be at the phosphorus atom of the ligand.[6] Thus a number of such chiral, monodentate phosphine ligands were prepared and used for the hydrogenation of α-acetoamidocinnamic acid



(1-3)

Table 1-1. Monodentate Phosphine Ligands for Structure-Selectivity Study

Entry	PR_3	ee %
1		28 (*S*)
2		28 (*S*)
3		32 (*S*)
4		58 (*S*)
5		88 (*S*)

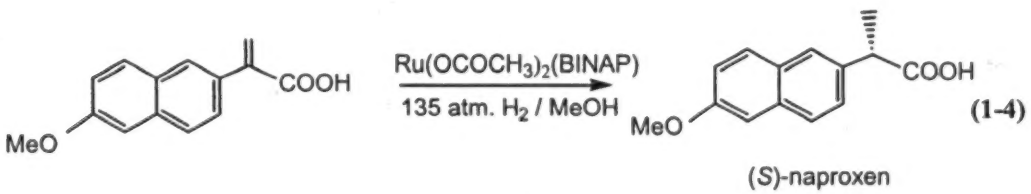
(MAC acid) as a test reaction (equation 1-3). This hydrogenation step is key to the synthesis of L-DOPA, a drug for treatment of Parkinson's disease.[6] A structure variation study of the substituents on the phosphorus atom improved the selectivity of the monophosphine ligands to 88 % ee (Table 1-1 entry 5).[6] These findings stimulated

interest in this area of research and a number of chiral monodentate ligands were developed for asymmetric hydrogenation usually with modest optical yields.[6]

A few of the early monodentate chiral phosphines gave good ee values for the hydrogenation of MAC acid[6] and de Vries *et al.*[7] have recently developed a series of monodentate chiral phosphines that give high ee values for the hydrogenation of a variety of substrates. The majority of the work, however, involves use of diphosphine ligands that have a higher probability of obtaining high ee values. Thus, a number of chelating phosphines such as BPPM,[8] DIPAMP,[9] CHIRAPHOS,[10] NORPHOS,[11] and DUPHOS,[12] were synthesized and used for the Rh catalyzed asymmetric hydrogenation of acylaminoacrylic acids. The early emphasis was on Rh-based catalysis since these systems were relatively easy to prepare and gave good selectivities in hydrogenation of acylaminoacrylic acids.[6] When the scope of this catalysis was extended to other substrates, for example functionalized ketones, rhodium-based catalysts were found wanting and other transition metals, especially ruthenium, were investigated.

The first to report a ruthenium-based catalyst for asymmetric hydrogenation was James *et al.* who prepared the complex $Ru_2Cl_4(DIOP)_3$ by reaction of $RuCl_2(PPh_3)_3$ with DIOP.[13] This catalyst gave 60 % ee for the hydrogenation of α-acetamidoacrylic acid, which was modest compared to the selectivities that could be obtained by rhodium catalysts at the time, for example 96 % ee could be obtained using $RhCl(PPh_3)$ (DIPAMP).[9] The discovery of BINAP by Noyori *et al.*[14] revolutionized the role of ruthenium metal in asymmetric hydrogenation. There are now many reports detailing the synthesis and use of ruthenium complexes for asymmetric hydrogenations.[15] Only generally illustrative ruthenium systems will be discussed here.

The BINAP dicarboxylate complexes of the type (BINAP)Ru(OCOR)$_2$ (R = CH_3, $C(CH_3)CHCH_3$, $C(CH_3)_3$, $CH(CH_3)CH_2CH_3$)[16] are efficient for the asymmetric hydrogenation of various types of olefinic bonds and are used for the preparation of a wide range of biologically important molecules. For example, the anti-inflammatory drug naproxen can be synthesized in 97 % ee using these hydrogenation catalysts (equation 1-4).[17]



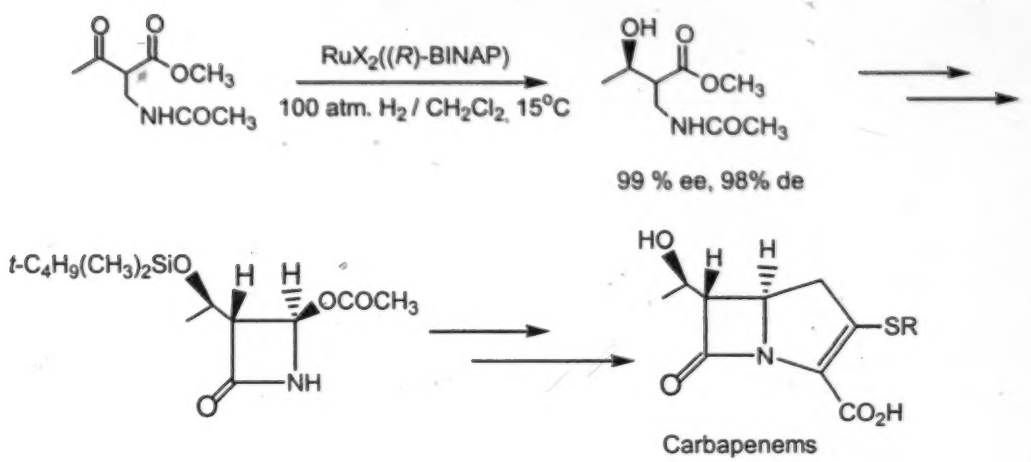
(1-4)

(*S*)-naproxen

The halide complexes "RuX_2(diphosphine)" (X = Cl, Br) are often generated *in situ* by addition of HX to either the dicarboxylate complexes[18] or the bis(allyl) complexes of the type Ru(η^3-allyl)$_2$(diphosphine).[19] These compounds are also obtained by reacting the complexes [RuX_2(η^6-arene)]$_2$ (η^6-arene = benzene, *p*-cymene, triphenyl stibine) with the appropriate diphosphine.[20] These complexes are important as catalyst precursors for the hydrogenation of a wide range of functionalized ketones containing heteroatoms such as oxygen, nitrogen or halogens that can chelate to Ru with the carbonyl group. This technology has been used for the synthesis of a number of biologically important molecules[21,22,23] including the synthesis of carbapenem antibiotics by Takasago International Co. (Scheme 1-1).[24]

The ruthenium complexes $RuCl_2$(diphosphine)(diamine).[25,26,27] have very high activities and enantioselectivities for reduction of ketones even at substrate:catalyst ratios upto 100,000:1.[27] Industrial application of these catalysts include the production

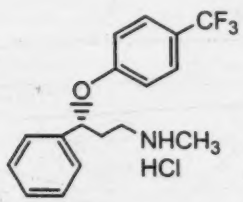
Scheme 1-1. Synthesis of carbapenem antibiotics



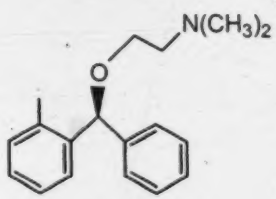
of the antidepressant agent fluoxetine hydrochloride,[28] and the antihistaminic drugs (*S*)-orphenadrine and (*R*)-neobenodine[29] shown in Scheme 1-2.

Ruthenium-based catalysis is wide in scope and has a lot of application in industry. However, there remain major challenges to be overcome. For example, ruthenium is quite toxic, so separation of catalyst residues from product molecules is crucial to the pharmaceutical and fragrance industry. Furthermore, it is becoming increasingly unsustainable to throw away these expensive catalysts after a single use. Despite these unavoidable concerns, there are only a few examples of reusable polymer-bound hydrogenation catalysts and none of which is prepared by ROMP. Also, all available precursors prior to this work do not react with a wide variety of diphosphines. In fact most of them are good only for BINAP and structurally related diphosphines; hence the need for more precursors that have a wider scope.

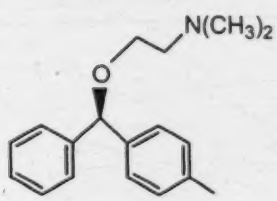
Scheme 1-2. Some important compounds obtained by Ru-diamine catalyzed hydrogenation



fluoxetine hydrochloride



(*S*)-orphenadrine



(*R*)-neobenodine

The lack of a general starting material for the preparation of ruthenium diphosphine complexes could be one of the reasons why ruthenium based catalysis lagged behind rhodium catalysis in the early developmental stages of asymmetric hydrogenation. The rhodium complexes $[Rh(diene)Cl]_2$[30] and $[Rh(diene)_2]X$ (diene = NBD or COD; X = BF_4^- or PF_6^-)[31] act as general precursors for the preparation of rhodium-diphosphine complexes. No such general ruthenium precursors exist and as a result, researchers have come up with a variety of complexes that are good for specific phosphines but lack generality. Some commonly used synthons include the complexes of ruthenium with monodentate phosphines such as $RuCl_2(PPh_3)_3$[13,32,33,34] and $RuCl_3(PPh_3)_2$,[33] the polymeric $[RuCl_2(COD)]_n$,[35,36,37] $Ru(\eta^3\text{-allyl})_2(COD)$,[38] and $[RuX_2(\eta^6\text{-arene})]_2$ (X = Cl, Br).[39] The preparation and use of these precursors, as well as their limitations, will be discussed in greater detail in Chapter 2.

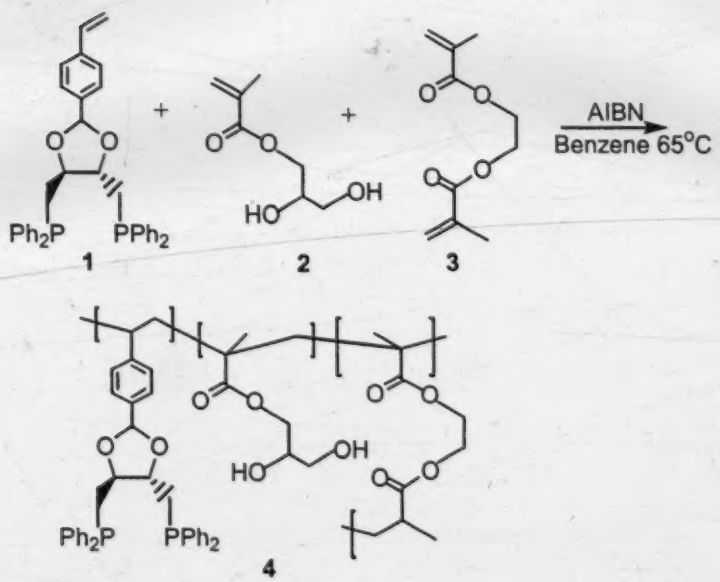
Rationale for immobilization and recycling of catalyts. The diphosphine ligands and the transition metals used in the preparation of catalysts precursors for homogeneous asymmetric hydrogenation are expensive. Industrial processes require

that production costs be minimized as much as possible. Thus the reuse of these catalysts is highly desirable. Furthermore, separation of catalyst from product may constitute a significant fraction of the production costs and hence easy product separation is very essential. In cases where the products formed are for human consumption, even minute contaminants could be harmful and care must be taken to ensure purity of the products. Future research in homogeneous catalysis may well shift to finding methods of immobilizing or heterogenizing these catalysts for economic and environmental reasons rather than focus on the development of novel homogeneous systems. Already a number of strategies and techniques for catalyst immobilization are in existence.[40] The oldest and by far the most commonly used technique is immobilization on organic polymers.[41] Immobilization on organic supports is achieved using one of the following types of reactions: radical copolymerization of vinyl derivatives of arenes and phosphines,[42] condensation reactions between acid derivatives and amines or alcohols,[43,44] condensation polymerization reactions between diamines and diisocyanates,[45] and Suzuki type couplings.[46]

Preparation and use of polymeric catalysts in asymmetric hydrogenation. Radical copolymerization of vinyl derivatives of arenes and phosphines was the method of choice for the preparation of one of the earliest successful polymeric catalyst for asymmetric hydrogenation. Stille *et al.*[42e] prepared a DIOP-like ligand **1** (scheme 1-3) that was obtained from DIOP by ethanolysis followed by reaction with 4-styryl benzaldehyde. Ligand **1** was then copolymerized with monomer **2** and a cross linker **3** using AIBN as initiator to give the supported ligand **4**. Ligand **4** and $[Rh(COD)Cl]_2$ were reacted *in situ* to generate a catalyst for the hydrogenation of MAC acid. The

polymer supported catalyst gives 77 % ee that compares favorably to 81 % ee obtained by homogeneous catalysis using a Rh-DIOP catalyst. The authors claim that the catalyst could be reused several times though only 2nd run data is provided. The activity of the supported catalyst is only 20 % of the activity of the homogeneous catalyst. A second problem encountered while using this catalyst is that there is rapid loss of activity on continued use and the authors presume, this is due to hydrolysis of the ether groups in the polymer.

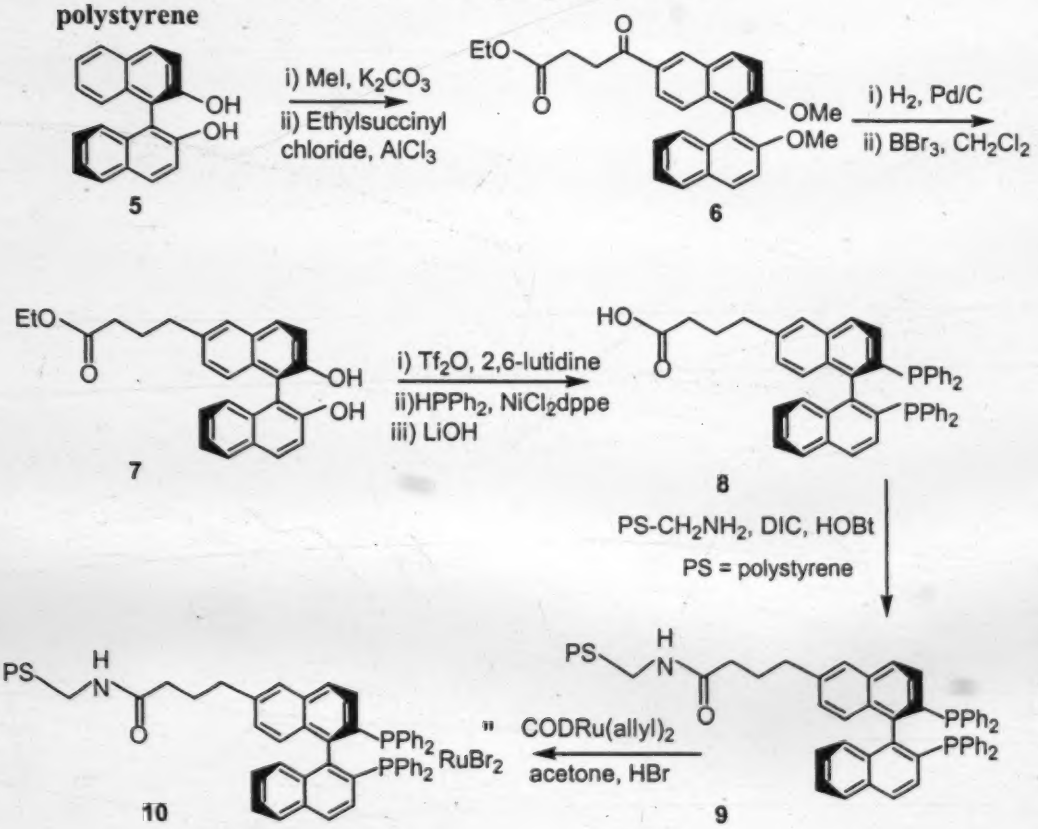
Scheme 1-3. Preparation of polymer supported DIOP



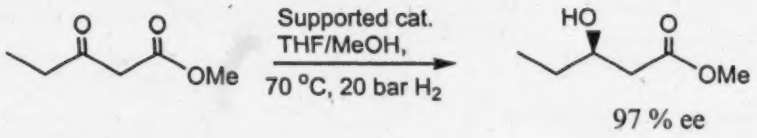
More recent work in polymer supported asymmetric hydrogenation has focused on heterogenization of ligands that are known to be effective in solution. Specifically,

BINAP has received a lot of attention because it is a ligand that gives high ee values in a variety of hydrogenation reactions using either Rh or Ru complexes.[43,44] The first supported BINAP was reported by Bayston *et al.*[43a] Their methodology involves the

Scheme 1-4. Derivatization and coupling of BINAP to polystyrene



preparation of a suitably functionalized BINAP monomer **8** (scheme 1-4) and its attachment to a commercially available amino polystyrene. Monomer **8** is prepared from BINOL **5** in three steps as shown in the scheme. Attachment to polystyrene is

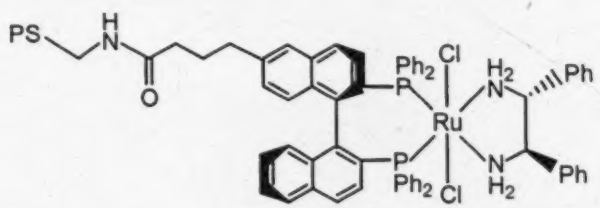


(1-5)

facilitated by the condensation reaction between the acid derivative on **8** and the amino group of the polymer. The resulting supported diphosphine **9**, that is now commercially available,[47] was converted into a Ru catalyst **10** by reaction with $Ru(COD)(allyl)_2$ and this catalyst was effectively used for the reduction of methyl propionyl acetate which proceeded with 97 % ee (equation 1-5) as compared to the 99 % ee obtained by homogeneous BINAP-Ru hydrogenation. The rates of hydrogenation using catalyst **10** were very close to those obtained using the homogeneous catalyst for the first run. However, the supported catalyst loses both activity and selectivity rapidly, with the 3rd run requiring 36 h to obtain 82 % conversion to product as compared to 99 % conversion in 18 h for the 1st run. The ee also drops from 97 % to 91 % from the 1st run to the 3rd run. Only three runs in total were done using catalyst **10**, presumably due to loss of activity with each repeated use.

The most successful use of ligand **9** was reported by Noyori *et al.*[48] Noyori prepared the $RuCl_2$(diphosphine)(diamine) type complex by sequential reaction of **9** with the precursor $[RuCl_2(\eta^6\text{-benzene})]_2$ followed by (*R*,*R*)-DPEN to produce the supported catalyst **11** (figure 1-1). Catalyst **11** was used for the asymmetric hydrogenation of 1'-acetonapthone and gives 98 % ee that compares favorably with the 97 % ee obtained with the homogeneous catalyst. Catalyst **11** was reused a total of 13 times in this study and the ee values of the alcohol product varied between 97 % and 98

%. No rate comparisons were made between catalyst **11** and the homogenous catalyst. A major drawback of the supported catalyst is that polystyrene does not swell in polar

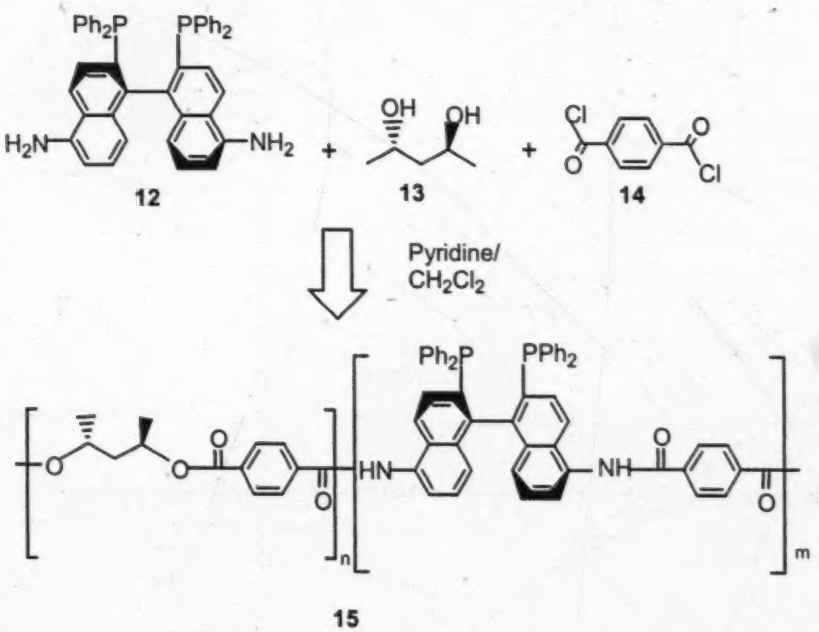


11

Figure 1-1. Polystyrene supported catalyst for ketone hydrogenation.

protic solvents such as 2-propanol,[42b] the solvent of choice for the hydrogenation of alkyl-aryl ketones.[14d,e] Hydrogenation reactions using the polystyrene supported catalyst were therefore carried out in presence of DMF as a co-solvent that would cause the polystyrene resins to swell. The requirement for a co-solvent limits the applicability of the catalyst as DMF is not a widely used solvent in asymmetric hydrogenation and is also toxic.[49] For reasons that are not yet explained, the hydrogenation reactions using **11** were carried out with very high amounts of base relative to the Ru metal (50:1) as compared to 2:1 that is required to effect such hydrogenations.[14d] The catalyst lost its activity on continued use and the time required to obtain 100 % product for the 10th run (84 h) was more than four times that required for the 2nd run (20 h). Despite these drawbacks catalyst **11** is, to the best of my knowledge, the only supported asymmetric hydrogenation catalyst that has been reused more than ten times.

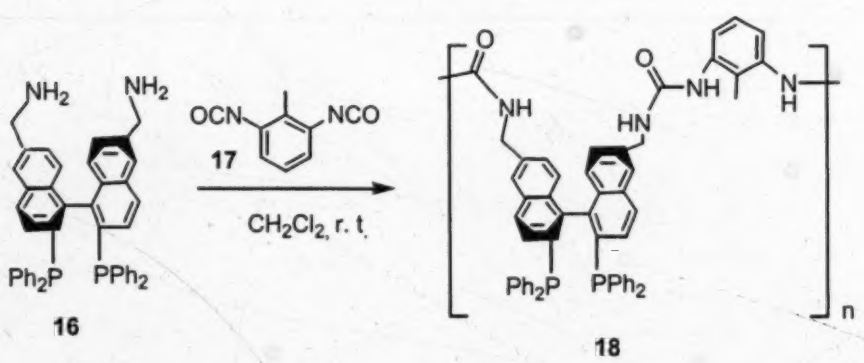
Scheme 1-5. Chan's synthesis of polymeric BINAP



Chan *et al.*[44] have described the preparation of the soluble linear polymeric BINAP derivative, **15**, which was prepared from the condensation of 5,5'-diamino-BINAP ligand (**12**) with (2*S*,4*S*)-pentanediol (**13**) and terephthalyol chloride (**14**) (Scheme 1-5). The metal was introduced *in situ* using $[RuCl_2(p\text{-cymene})]_2$ as the precursor. The utility of the supported catalyst was demonstrated in the asymmetric hydrogenation of 2-(6-methoxyl-2-napthyl)propenoic acid to the anti-inflammatory drug naproxen (equation 1-4). For hydrogenation reactions done using methanol-toluene mixtures (2:1 v/v) at 110 atm. H_2 pressure, 2 °C, the supported catalyst gave exactly the same ee value as the homogeneous catalyst (94 %). However, the supported

catalyst was more active (TOF = 32.1 h^{-1}) as compared to the unsupported system (TOF = 28.3 h^{-1}). Furthermore, the catalyst system was reused a total of ten times without significant loss in either activity or selectivity. The higher rates of reaction for the supported catalyst have been attributed to the presence of large polyester chains on the BINAP ligand that alter its dihedral angle in such a way as to increase its reactivity.[44] Recovery of the catalyst after reaction is by filtration after precipitation using methanol. This recovery procedure is slow and tedious and may be a big disadvantage in an industrial set-up.

Scheme 1-6. Lemaire's synthesis of polymeric BINAP



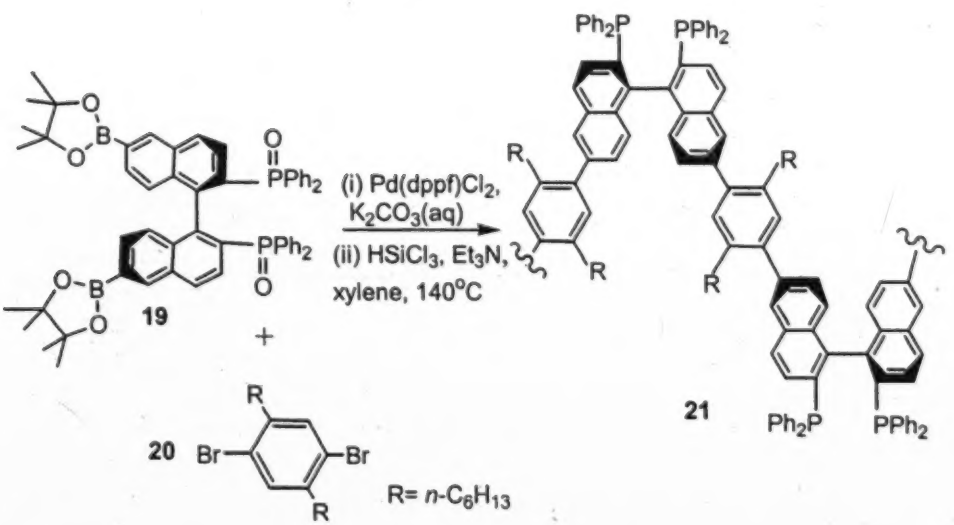
Lemaire *et al.*[45] have also prepared a linear polymeric (*S*)-BINAP derivative **18** (Scheme 1-6) which was obtained from the polycondensation of bisaminomethylated (*S*)-BINAP (**16**) with 2,6-diisocyanatotoluene (**17**). The active catalyst was generated *in situ* by reacting **18** with $[RuCl_2(benzene)]_2$ as the metal precursor and (*S,S*)-DPEN to produce what the authors believe is a $RuCl_2$(diphosphine)(diamine) type complex. The supported catalyst was used for the hydrogenation of acetophenone and 1'-acetonapthone at 3 atm. H_2 pressure, 40 °C and substrate to catalyst ratio 1000:1. The

acetophenone hydrogenation proceeded with a lower selectivity (68 % ee) as compared to 81 % ee obtained with the homogeneous catalyst under the same conditions.[45b] The hydrogenation of 1'-acetonapthone proceeded with the same ee (96 %) as for the homogeneous hydrogenation. The relative rates of hydrogenation using the supported catalyst and the homogeneous catalyst are not given. Reuse of the catalyst is demonstrated for acetophenone hydrogenation and a total of four runs were carried out. The catalyst displays a gradual decrease in selectivity with each run, the 4th run giving 61 % ee as compared to 68 % ee obtained for the first run.

Suzuki coupling has also been used as a technique for supporting BINAP. This technique was first used by Pu *et al.*[46] who prepared a derivatized chiral binapthyl monomer, **19** which was coupled to **20** followed by reduction of the phosphinoxy groups with trichlorosilane to produce poly (*R*)-BINAP **21** (scheme 1-7). Poly (*R*)-BINAP is soluble in most common organic solvents and is therefore used under homogeneous conditions and recovered by precipitation.[46c] Two categories of substrates were hydrogenated using poly (*R*)-BINAP as the ligand. The first category was the α-acylamino acrylic acids. For hydrogenation of these substrates the active catalyst was generated *in situ* by reacting **21** with the metal precursor $[Rh(COD)_2]BF_4$ in THF. The resulting catalyst suspension was tested for the hydrogenation of methyl α-(benzamido) cinnamate. This hydrogenation proceeded with 75 % ee that is comparable to 76 % ee obtained by homogeneous BINAP-Rh catalysis done under the same conditions. The supported catalyst was reused only once without loss of activity or selectivity. The second category of substrates that were hydrogenated using a polyBINAP catalyst are the aryl-alkyl ketones. A representative ketone from this category is acetophenone. For

the hydrogenation of this substrate, the catalyst was again generated *in situ*, by reaction of polyBINAP and the metal precursor $[RuCl_2(benzene)]_2$. (*R*,*R*)-DPEN was then added to the reaction to form $RuCl_2$(polyBINAP)(*R*,*R*)-DPEN (**22**). The hydrogenation of acetophenone using **22** proceeded with 80 % ee that compares closely with 81 % ee obtained using unsupported BINAP. No data is provided for reuse of the polymeric catalyst.

Scheme 1-7. Pu's soluble polymeric BINAP ligand



The work reviewed above demonstrates that heterogenization and reuse of homogeneous catalysts is possible. For soluble polymer bound systems, the rates and activities tend to be comparable to those of the unsupported systems,[44,50,51] however these systems lack the advantage of easy recovery as they must be precipitated from the reaction mixture and filtered. In the case of insoluble polymers, their rates and selectivity tend to be lower than those of the homogeneous system, or lose activity rapidly on reuse.[42] To improve the activity of insoluble polymer bound systems, aprotic

solvents have been used.[48] Such solvents improve the swelling of the polymer in solution, however they may also limit the scope of substrates that can be hydrogenated by such polymer bound systems. Overall, there is still work to be done to improve the activity, selectivity and reusability of supported asymmetric hydrogenation catalysts.

Research objectives. After more than three decades since the discovery of asymmetric hydrogenation, there is still no known way of determining before hand what the selectivity of any given phosphine for the hydrogenation of a specified substrate would be. The only known way is to do a systematic variation of catalyst structure, reaction conditions and then observe the ee obtained. Such a study is greatly simplified when a metal complex that reacts with a large variety of diphosphine ligands to produce well-defined, active catalyst precursors is available. In an industrial setting where the target is the development of a catalyst for asymmetric hydrogenation of a specified substrate, the approach is to obtain a number of diphosphine ligands and screen them in order to determine which one gives the best selectivities for the target reaction. In fact this was the process used by Knowles *et al.* in the development of the first commercial asymmetric hydrogenation catalyst (see Table 1-1).[6] In addition, if the products of the reaction between the phosphines and the synthon are well-defined complexes, then it is easier to study the mechanism of the reaction.[52] The first objective of this study was therefore to synthesize a ruthenium catalyst synthon, that can be used with a broad range of diphosphine ligands. The complex used as starting material should be relatively air-stable and easy to handle in addition to forming well-defined ruthenium complexes that can be used for mechanistic studies. This thesis describes the results obtained in our endeavor to prepare such a ruthenium complex.

The second objective of this study was to prepare supported ruthenium catalyst precursors that could be reused in asymmetric hydrogenations. It should be noted that in all the above-mentioned methodologies, the supported ligand is prepared first before being reacted with the appropriate metal complex to form the catalyst precursor. In most cases it is difficult to know if all the phosphine sites are metallated. It is very important that all phosphine sites be metallated because most hydrogenation reactions proceed by phosphine dissociation from the metal to generate a vacant site for substrate binding. The presence of uncoordinated phosphines within the polymer matrix can, potentially, act as a poison by coordinating to the vacant site and thereby shutting off the catalytic activity of the metal. It is also important that the presence of other carbon-heteroatom bonds within the polymer matrix be avoided for two reasons. First, such atoms are capable of coordinating to the metal and shutting off the catalyst or cross-linking the polymer. Secondly carbon-heteroatom bonds are reactive and can be easily cleaved by for example hydrolysis. They therefore act as a weak link in the polymer chain. It is reasonable therefore to believe that a superior method for preparation of polymer supported catalysts should involve polymerization of a diphosphine ligand already attached to the metal. This type of polymerization would avoid problems associated with linker groups and guarantees that all phosphine sites within the polymer are coordinated to the metal. One possible methodology by which this type of polymerization can be done is by Ring Opening Metathesis Polymerization (ROMP). The use of ROMP supported reagents in organic syntheses is now widespread,[53] however, their use in asymmetric hydrogenation is reported for the first time in this thesis.

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Chapter 2†

A Versatile Precursor to Ruthenium-Diphosphine Hydrogenation Catalysts

Introduction

Complexes of ruthenium(II) with chiral diphosphine ligands are among the most successful catalyst systems for enantioselective hydrogenation of prochiral olefins and ketones.[1] The first such complex was prepared and used for asymmetric hydrogenation by James *et al.* in 1975.[2] Since then a large number of these complexes have been prepared and used as catalyst precursors for the hydrogenation of a wide range of prochiral substrates. A variety of olefinic substrates, including α,β-or β,γ- unsaturated carboxylic acids and allylic alcohols can be hydrogenated in high rates and enantioselectively. Ketonic substrates are hydrogenated under mild conditions in high chemo- and enantioselectivities by these systems as well. One of the challenges encountered in the synthesis of these catalysts is that there are no ruthenium complexes that can be used as a general starting material for preparation of ruthenium-diphosphine complexes. As

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will be discussed, there are ruthenium complexes that work well with a narrow distribution of diphosphine ligands. This area of research would greatly benefit from a ruthenium complex, that would react with most types of diphosphine ligands to generate well-defined catalyst precursors. Such a complex would allow more efficient and conclusive rapid screening of chiral diphosphine ligands for a desired catalytic hydrogenation. The search is still on for such complexes that would give universal reactivity with diphosphine ligands. Toward this end, various workers have come up with different procedures and strategies. The procedures that have been used most can be divided into the following broad categories: (i) phosphine exchange reactions; (ii) direct reaction of polymeric $[RuCl_2(COD)]_n$ with diphosphine ligands; (iii) displacement of COD by diphosphine ligands from mono- or dinuclear 'Ru-COD' complexes; (iv) reaction of 'Ru-η^6-arene' complexes with diphosphine ligands; (v) substitution of acac by diphosphine ligands from $Ru(acac)_3$.

Phosphine exchange reactions refer to the substitution of monodentate phosphine ligands by diphosphines. This procedure was first used in the preparation of $Ru_2Cl_4(DIOP)_3$ by reaction of $RuCl_2(PPh_3)_3$ with DIOP.[2] Most of the work that has been reported in this area is by the James' group.[3] The commonly used synthons for phosphine exchange are $RuCl_2(PPh_3)_3$ and $RuCl_3(PPh_3)_2(DMA)\bullet DMA$. The type of product(s) obtained from reaction of $RuCl_2(PPh_3)_3$ and diphosphine ligands depend

$$2RuCl_2(PPh_3)_3 + 3(P\text{-}P) \longrightarrow Ru_2Cl_4(P\text{-}P)_3 + 6PPh_3 \qquad \textbf{(2-1)}$$

$$RuCl_2(PPh_3)_3 + (P\text{-}P) \longrightarrow RuCl_2(P\text{-}P)(PPh_3) + 2PPh_3 \text{ for } n = 4 \qquad \textbf{(2-2)}$$

$$2RuCl_2(PPh_3)_3 + 2(P\text{-}P) \longrightarrow Ru_2Cl_4(P\text{-}P)_2 + 6PPh_3 \text{ for } n \leq 3 \quad \textbf{(2-3)}$$

$$4RuCl_3(PPh_3)_2 + 4(P\text{-}P) + H_2O \longrightarrow 2Ru_2Cl_5(P\text{-}P)_2 + OPPh_3 + 7PPh_3 + 2HCl \quad \textbf{(2-4)}$$

$$Ru_2Cl_5(P\text{-}P)_2 + 0.5H_2 \longrightarrow Ru_2Cl_4(P\text{-}P)_2 + HCl \quad \textbf{(2-5)}$$

$$(P\text{-}P) = PPh_2(CH_2)_nPPh_2 \ (n = 1\text{-}4)$$

on both the structure of the diphosphine and the reaction stoichiometry. When excess diphosphine is used, the product is of the type $Ru_2Cl_4(P\text{-}P)_3$ (P-P = diphosphine) (eq. 2-1). If a stoichiometric amount of the diphosphine ligand is used the product is of the type $RuCl_2(P\text{-}P)(PPh_3)$,[3c] for ligands that form seven-membered chelate rings (eq. 2-2), or $Ru_2Cl_4(P\text{-}P)_2$, for ligands that form smaller rings (eq. 2-3).[3h] Reaction of diphosphine ligands with $RuCl_3(PPh_3)_2(DMA)\bullet DMA$ generates the triply-bridged, mixed-valence compounds of the type $Ru_2Cl_5(P\text{-}P)_2$ (eq. 2-4). These mixed valence compounds are then reduced by H_2 to $Ru_2Cl_4(P\text{-}P)_2$ (eq. 2-5).[3c] Other examples of phosphine exchange reactions include the preparation of $RuCl_2(BIPHEMP)(PPh_3)$,[4] and $RuCl_2(PIGIPHOS)$[5] by the reaction of the respective diphosphine ligands and $RuCl_2(PPh_3)_3$. The complexes $RuCl_2(RCp)(PPh_3)_2$ (R = H, CH_3) have also been used as starting material for phosphine exchange reactions as they react with BINAP to give $RuCl_2(RCp)(BINAP)$.[6] More recently, Morris *et al.*[7] have shown that the complexes $RuCl(H)(PPh_3)_3$ and $RuCl(H)(diamine)(PPh_3)_2$ (diamine = cydn, DPEN) are useful starting materials for phosphine exchange with diphosphine ligands. There are, however, some limitations of phosphine exchange as a synthetic procedure to ruthenium

catalyst precursors in that not all types of diphosphine ligands displace PPh_3 from the ruthenium complexes[8,9] or the displacement reaction is not clean.

The polymeric complex $[RuCl_2(COD)]_n$ has been widely used as starting material for the preparation of Ru(II) complexes with chiral diphosphine ligands.[8,9,10] The preparative procedure often involves refluxing the polymeric complex in toluene in the presence of a diphosphine ligand and Et_3N. If BINAP or its substituted analogues are used, this procedure generates the anionic dinuclear complexes $[NH_2Et_2]^+[\{RuCl(P\text{-}P)\}_2(\mu\text{-}Cl)_3]^-$ (P-P = BINAP or substituted analogue), that are catalyst precursors for the enantioselective hydrogenation of olefins and ketones.[8,11] Reaction of $[NH_2Et_2]^+[\{RuCl(P\text{-}P)\}_2(\mu\text{-}Cl)_3]^-$ with NaOAc gives the dicarboxylate complexes $Ru(P\text{-}P)(OCOCH_3)_2$ that are highly enantioselective catalysts for hydrogenation of a wide variety of olefinic substrates, including α,β-unsaturated carboxylic acids.[10] This preparative route to Ru-diphosphine complexes has two major shortcomings. First, the chloro-bridged product obtained is always contaminated with side products resulting in low yield and purity.[8,9,10,11] For example, the complex $[NH_2Et_2]^+[\{RuCl(R)\text{-}p\text{-}MeO\text{-}BINAP\}_2(\mu\text{-}Cl)_3]^-$ is obtained in only 37% yield by this procedure and is usually contaminated by $RuHCl\{(R)\text{-}p\text{-}MeO\text{-}BINAP\}_2$.[11,12] Secondly, the procedure works only for BINAP and structurally related ligands. Diphosphine ligands such as BPPM, CHIRAPHOS, and NORPHOS do not react under similar conditions.[13]

There are several mono- or dinuclear ruthenium complexes that could be used as starting material for catalyst preparation. Most of these are COD containing ruthenium complexes since COD displacement by diphosphine ligands is perceived as a feasible reaction. Several such complexes have been prepared.[14] The most often used among

them is probably Ru(η^3-$CH_2C(CH_3)CH_2)_2$(COD).[15] The widespread use of this complex is due to the relative ease with which it is prepared[16] and also because COD displacement can be effected readily by various structurally different diphosphines ligands.[15] Reaction of chiral diphosphine ligands with this starting material is reported to produce complexes of the type Ru(η^3-$CH_2C(CH_3)CH_2)_2$(P-P*) (P-P* = chiral diphosphine ligand) which are active catalysts for olefin hydrogenation. This preparative method appears to work well for electron rich diphosphines ligands such as CHIRAPHOS, DIOP, and others,[15] but some of the products are not well characterized and electron deficient diphosphines, such as BINAP, give mixtures of products that are difficult to separate.[15c,15l]

It is an empirical observation that ketones having chelating heteroatoms close to the carbonyl group (functionalized ketones, including diketones, hydroxy ketones or ketoesters), require halogen-containing ruthenium complexes for efficient enantioselective reduction.[17] The Ru(η^3-$CH_2C(CH_3)CH_2)_2$(P-P*) type complexes obtained by displacement of COD from Ru(η^3- $CH_2C(CH_3)CH_2)_2$(COD) are inactive as catalysts for hydrogenation of these substrates. Procedures do exist for conversion of these complexes into halogen-containing species.[15c] Reaction of Ru(η^3- $CH_2C(CH_3)CH_2)_2$(P-P*) with HX (X = Cl, Br or I) in acetone gives poorly characterized species that have been formulated as [RuX_2 (P-P*)]$_2$(acetone).[15c,l] The halide species are usually generated *in situ* and used for hydrogenation of functionalized ketones. Their exact structure and composition are unknown.[15c] These halide species can also be obtained by addition of HX to Ru$(OCOR)_2$(P-P*),[17a,b] or by direct reaction of

diphosphine with $RuCl_3.3H_2O$ as recently reported by Genêt *et al.*[18] In both cases the products obtained are complicated mixtures.

Complexes of the type $[RuX_2(\eta^6\text{-arene})]_2$ (η^6-arene = benzene, *p*-cymene, triphenylstibine) have been used as starting material for generation of well defined and pure halogen-containing Ru-diphosphine complexes.[19] Reaction of certain diphosphine ligands with the dimeric arene complexes generates cationic species of the type $[RuX(P\text{-}P^*)(\eta^6\text{-arene})]^+$ that are highly efficient for hydrogenation of functionalized ketones. Furthermore, these complexes can easily be converted into the dicarboxylate complexes $Ru(OCOCH_3)_2(P\text{-}P^*)$, by refluxing in DMF in presence of NaOAc[10b] or the diamine complexes, $RuX_2(P\text{-}P^*)$(1,2 diamine).[20] However, the $[RuX_2(\eta^6\text{-arene})]_2$ complexes work well only when the diphosphine ligand is rigid and bulky.[19,21,22] Ligands containing alkyl backbone such as CHIRAPHOS, DIOP or dppb generally give mixtures of the desired product with contaminants, $[RuCl_2(\eta^6\text{-arene})]_2(\mu\text{-}P\text{-}P^*)$ and *trans*-$RuCl_2(P\text{-}P^*)_2$, where the arene group has been displaced.[23]

The complex $Ru(acac)_3$ has also been used as starting material for preparation of diphosphine complexes. Reaction of (P-P*) with $Ru(acac)_3$,[24,25] under reducing conditions, generates products of the type $Ru(acac)_2(P\text{-}P^*)$. This procedure is not as widespread as those discussed above probably due to the vigorous conditions required for the reduction. Usually high hydrogen pressure (1000 psi)[24] at ambient temperature or prolonged refluxing in the presence of Zn metal[25] is required for acac displacement to occur.

In the Bergens' Laboratories, research has focused on the synthesis and development of diphosphine ligands and catalyst precursors for asymmetric

hydrogenation and on mechanistic studies of the newly discovered catalysts.[26] These objectives demand that the starting material used for the preparation of the catalysts be versatile (react with a large variety of diphosphines ligands), gives catalysts which are active for a wide range of substrates, and above all, the products formed are pure. The reported catalyst precursors were found to be inadequate in terms of versatility, applicability, convenience and activity and purity of the resulting catalysts. Clearly a compound that could fulfill the above demands was required. Further, such a universal starting material is essential in cases where rapid screening of diphosphine ligands is required. Screening involves attachment of the diphosphine ligand to the Ru metal and use of the obtained complexes for hydrogenation of a specified substrate in order to determine the ligand that gives the best yields and selectivities. This chapter describes a versatile and convenient procedure for the synthesis of ruthenium-diphosphine catalyst precursors that complements the existing procedures in the literature. The synthesis uses a moderately air-stable ruthenium complex that reacts cleanly with a representative distribution of chiral diphosphine ligands. The resulting ruthenium-diphosphine catalyst precursors are mononuclear, crystalline species that can be characterized by solution NMR spectroscopy, and in some cases, by X-ray diffraction. Methodologies to screen these compounds for a representative variety of hydrogenation reactions are reported. Convenient one-step methodologies to convert the catalyst precursors into the diamine complexes RuX_2(P-P*)(1,2-diamine) are also reported.

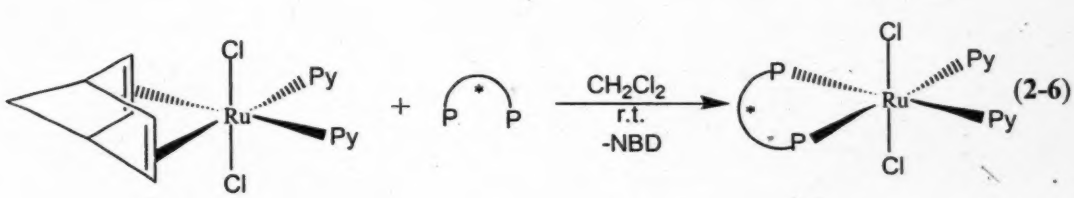
Results and Discussion

The known compound *trans*-$RuCl_2(NBD)Py_2$ (**1**),[27] was examined as a potential starting material for the preparation of Ru-diphosphine complexes because it is monomeric, contains NBD groups that are known to be readily displaced in Rh complexes such as $[Rh(diene)Cl]_2$ (diene =NBD, COD),[28] and also because it contains Cl^- ligands that are important in Ru asymmetric catalysis.[15c,17,18,19] Compound **1** can be prepared in high yield by stirring $[RuCl_2(NBD)]_n$[27] in pyridine solution at room temperature for one week followed by purification by chromatography on alumina in air using ethyl acetate as eluent. **1** can be obtained in shorter times as described in the literature[27] by heating finely-ground $[RuCl_2(NBD)]_n$ in Py solution at 100 °C with rapid stirring until the starting material dissolves (usually in less than one hour). However, heating at this temperature until the $[RuCl_2(NBD)]_n$ is dissolved causes formation of appreciable amounts of *trans*-$RuCl_2Py_4$ by displacement of NBD in **1** by Py. The amount of *trans*-$RuCl_2Py_4$ formed varied from batch to batch of $[RuCl_2(NBD)]_n$. Batches that dissolved quickly formed negligible amounts of *trans*-$RuCl_2Py_4$. Batches that required heating for longer periods of time formed more *trans*-$RuCl_2Py_4$. It was most convenient to prepare **1** by stirring the reaction mixture at room temperature for one week, a procedure that never failed to produce **1** in high yields. Thus obtained, **1** is pure, thermally stable, and survives exposure to air for weeks without oxidation. These properties allowed preparation and storage of large amounts of **1** for use as required for later experiments.

A single-crystal X-ray structural analysis of **1** was carried out to investigate the nature and coordination of this compound. The analysis shows that this compound is mononuclear hexacoordinate ruthenium(II) with the NBD ligand η^4-bonded to ruthenium. The Cl^- ligands occupy a mutually *trans* disposition while the Py ligands

are *cis* to each other as shown in figure 2-1. The average bond length of 2.192 Å between ruthenium and the olefinic carbon atoms is very similar to those reported for hexacoordinate Ru(II) complexes containing η^4-NBD ligands such as $RuCl_2(NBD)(Pip)_2$,[27] $RuCl_2(NBD)(PPh_3)_2$,[29] $RuCl\{2,6\text{-}(Me_2NCH_2)_2C_6H_3\}(NBD)$[30] and $RuH\{2,6\text{-}(Ph_2PCH_2)_2C_6H_3\}(NBD)$.[31] The structure of **1** can be best described as a distorted octahedral in which two vertices are occupied by the double bonds of the NBD ligand causing great distortions from the regular octahedral structure. Due to ligand constrain, the angles between the two olefin bonds, C2-Ru-C6 or C3-Ru-C5, are approximately 66°, off from the 90° for a regular octahedral, but are within the range reported for such compounds.[29,30,31] The Ru-Cl and Ru-N distances are within the expected range for similar compounds.[27,29] The bond lengths C2-C3 (1.396(8)) Å and C5-C6 (1.370(9)) Å indicate that these are double bonds. The deviation of the Cl1-Ru-Cl2 angle, approximately 163°, from the expected 180°, has been attributed to the unfavorable steric interactions between the Cl^- ligands and the olefinic hydrogens on the NBD ligand for related compounds.[27] This interaction causes a slight bend in the Ru-Cl bonds leading to a decrease in C11-Ru-Cl2 angle. Some bond lengths and angles relevant to compound **1** are shown in table 2-1.

Compound **1** reacts with the diphosphine ligands (*R*)-BINAP, (*S*,*S*)-CHIRAPHOS, (*S*,*S*)-SKEWPHOS, (*R*,*R*)-NORPHOS or (*R*,*R*)-Me-DUPHOS) over 12 h at room temperature in CH_2Cl_2 to generate in high yields the corresponding



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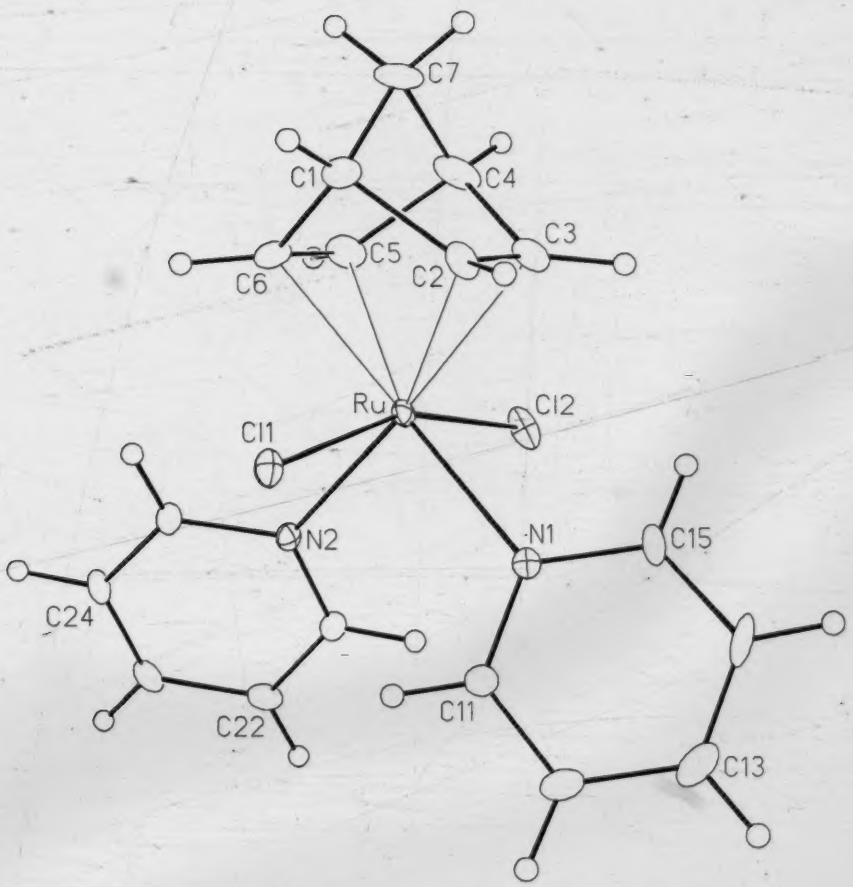


Figure 2-1. A perspective view of **1** showing the atom numbering scheme.

Table 2-1. Selected Interatomic Distances (Å) and Angles (deg) for *trans*-$RuCl_2(NBD)Py_2$ (1)

Ru–Cl1	2.4228(14)	C1–C7	1.513(10)
Ru–Cl2	2.4342(14)	C2–C3	1.396(8)
Ru–N1	2.160(4)	C3–C4	1.537(9)
Ru–N2	2.154(4)	C4–C5	1.545(9)
Ru–C2	2.196(5)	C4–C7	1.550(10)
Ru–C3	2.193(6)	C5–C6	1.370(9)
Ru–C5	2.180(6)	C11–C12	1.376(8)
Ru–C6	2.200(6)	C12–C13	1.374(9)
Cl1–Ru–Cl2	162.65(5)	N1–Ru–N2	92.4(2)
Cl1–Ru–N1	83.66(11)	N1–Ru–C2	98.4(2)
Cl1–Ru–N2	84.60(11)	N1–Ru–C3	99.6(2)
Cl1–Ru–C2	78.8(2)	N1–Ru–C5	160.0(2)
Cl1–Ru–C3	115.8(2)	N1–Ru–C6	157.9(2)
Cl1–Ru–C5	114.5(2)	C2–Ru–C3	37.1(2)
Cl1–Ru–C6	78.2(2)	C2–Ru–C5	78.1(3)
Cl2–Ru–N2	83.97(11)	C2–Ru–C6	65.9(2)
Cl2–Ru–C2	115.0(2)	C3–Ru–C5	65.6(2)
Cl2–Ru–C3	78.2(2)	C3–Ru–C6	77.5(2)
Cl2–Ru–C3	80.0(2)	C5–Ru–C6	36.4(2)

complexes *trans*-$RuCl_2$(P-P*)Py_2 (eq. 2-6). The complexes were mostly obtained as crystalline solids by recrystallization. This series contains representatives of the biaryl-bridged (BINAP), the arene-bridged (Me-DUPHOS), the methylene chain-bridged (CHIRAPHOS, SKEWPHOS), and the norbornyl-bridged type (NORPHOS) of chiral diphoshine ligands. The *trans*-$RuCl_2$(P-P*)Py_2 products are moderately air-stable, but those containing electron-rich phosphines are susceptible to air oxidation over time. In all complexes studied (except for NORPHOS complexes) the phosphorus centers are equivalent by NMR spectroscopy, showing that the Py ligands are either mutually *trans,* or they are both *trans* to the phosphorus centers. Figures 2-2 and 2-3 shows the X-ray structures of *trans*-$RuCl_2$((*R*)-BINAP)Py_2 (**2**) and *trans*-$RuCl_2$((*S,S*)-CHIRAPHOS)Py_2 (**3**) respectively. In both compounds, the geometry around the ruthenium atom is distorted octahedral defined by the chloride ligands, the two phosphorus atoms of the diphosphine ligands and the two Py ligands. The Py ligands are mutually *cis* whereas the Cl^- ligands are *trans* to one another. In compound **2**, the dissymmetric (*R*)-BINAP ligand forms a skewed, seven membered chelate ring which is fixed in a λ conformation.[32a,b] In the solid state, this causes the orientation of the phenyl substituents on the two phosphorus atoms to be arranged in an alternating edge-face manner as shown in figure 2-2. The Ru-P, Ru-N, Ru-Cl bond distances in **2** are all within the range reported for related ruthenium-BINAP complexes.[32] Likewise the bite angle, P1-Ru-P2, for the BINAP ligand obtained for compound **2** (89.15(12)°) is well within the range expected for Ru(II)-BINAP complexes (86-93.2°).[32c,e] Some selected interatomic distances and angles for **2** are given in Table 2-2.

The (*S,S*)-CHIRAPHOS ligand coordinates to the ruthenium metal in a δ conformation in compound **3** as shown in figure 2-3. The δ conformation is preferred because of the (*S,S*) chirality of the C1 and C2 atoms. A λ conformation would require the methyl groups on C1 and C2 to be in axial positions rather than the observed equatorial positions, a situation that would increase steric crowding.[33c] Once again, the

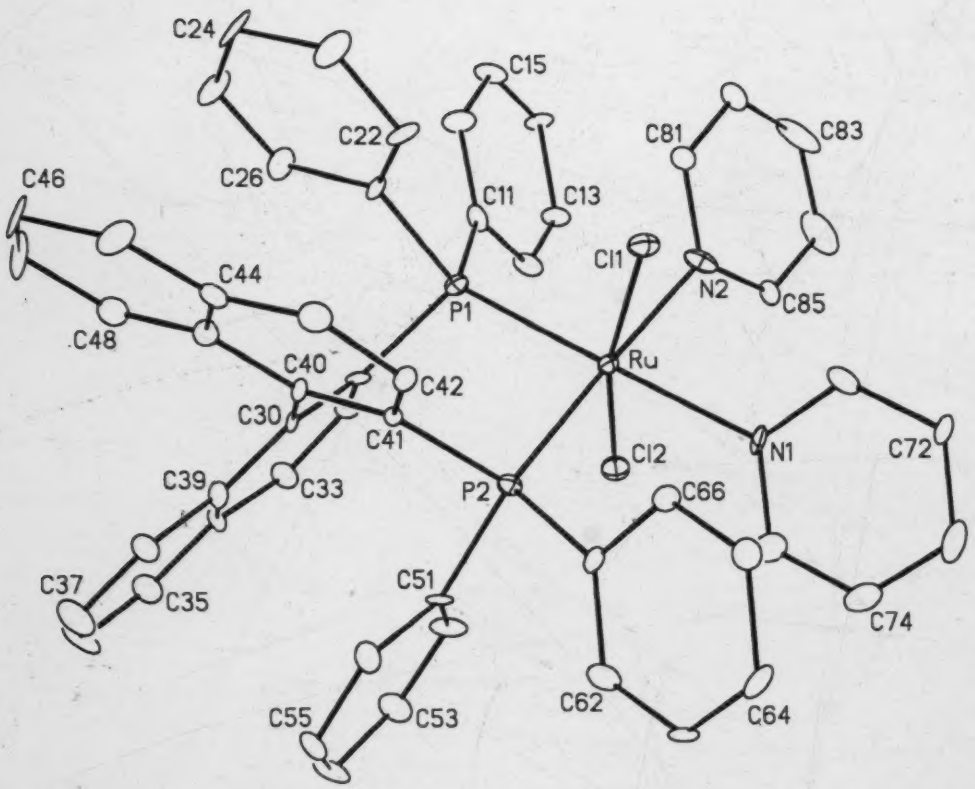


Figure 2-2. A perspective view of **2**•2CH_2Cl_2 showing the atom numbering scheme. All hydrogen atoms have been omitted for clarity.

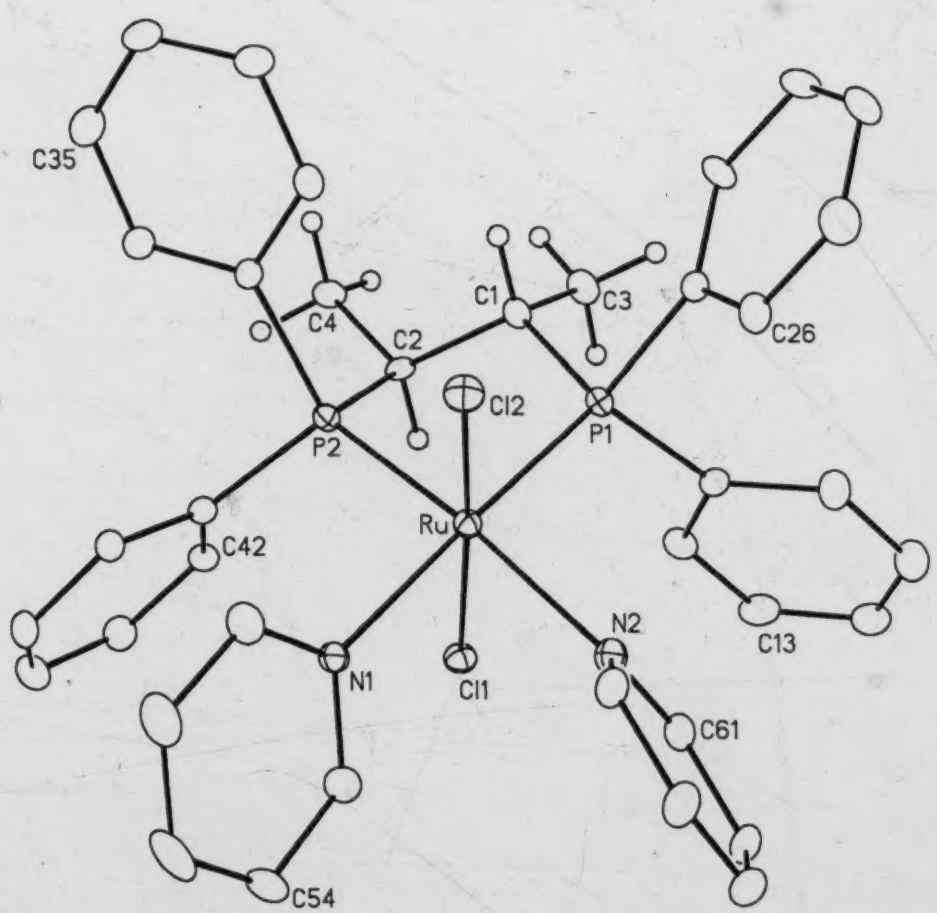


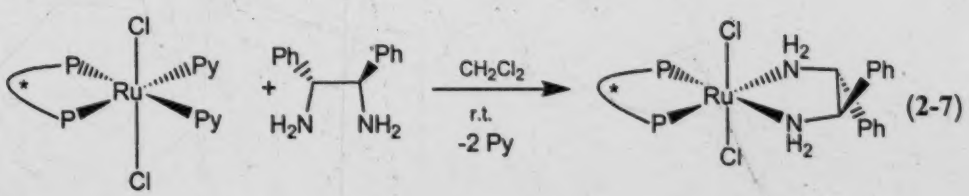
Figure 2-3. A perspective view of **3** showing the atom numbering scheme. Hydrogen atoms are shown with arbitrarily small thermal parameters for aliphatic groups (C(1), C(2), C(3), C(4)) and are not shown for the phenyl groups.

Table 2-2. Selected Interatomic Distances (Å) and Angles (deg) for 2 and 3

	2	3
Ru–Cl1	2.419(3)	2.406(14)
Ru–Cl2	2.432(3)	2.402(2)
Ru–P1	2.325(3)	2.2671(14)
Ru–P2	2.314(3)	2.2622(14)
Ru–N1	2.176(10)	2.209(4)
Ru–N2	2.144(11)	2.198(4)
P1–C11	1.846(12)	1.843(5)
P1–C21	1.841(12)	1.826(5)
Cl1–Ru–Cl2	167.28(10)	173.36(6)
Cl1–Ru–P1	95.57(12)	91.28(5)
Cl1–Ru–P2	93.34(12)	84.28(5)
Cl1–Ru–N1	85.0(3)	87.58(11)
Cl1–Ru–N2	84.9(3)	87.82(12)
Cl2–Ru–P1	94.00(12)	95.12(5)
Cl2–Ru–P2	95.16(12)	98.12(5)
Cl2–Ru–N1	85.2(3)	85.97(11)
Cl2–Ru–N2	86.2(3)	89.61(12)
P1–Ru–P2	89.15(12)	83.93(5)

phenyl substituents on the two phosphorus atoms adopt an edge-face conformation in the solid state. This edge-face conformation of the phenyl substituents has been given as the reason why chiral diphosphine ligands give high selectivities in asymmetric reactions. It is argued that the coordinated substrate molecule is exposed to the edge of the phenyl group on one side and to the face of the phenyl group on the opposite side, which leads to diastereoselection.[33d] This argument, though plausible, may not be entirely true as recent work by Bergens *et al.*[26a] has shown that there is rapid rotation about the P-Ph bonds in Ru-BINAP complexes, even at –30 °C. Thus this rigid face-edge conformation of phenyl groups may not exist in solution at least for the BINAP complexes. In fact, the fluxional nature of the phenyl groups may explain why xylBINAP has higher selectivity for hydrogenation of aryl-alkyl ketones as compared to BINAP[1i] as the former diphosphine would be expected to have a higher energy barrier to rotation about P-Ph bonds. The Ru-P, Ru-N and Ru-Cl in compound **3** are all within the range reported for related ruthenium-CHIRAPHOS compounds.[33] Some selected bond distances and angles for this compound are shown in Table 2-2.

Reaction of all the *trans*-$RuCl_2(P\text{-}P^*)Py_2$ complexes with DPEN at room temperature over 2h in CH_2Cl_2 resulted in quantitative or near quantitative displacement of the pyridine ligands to form *trans*-$RuCl_2(P\text{-}P^*)$ DPEN (eq. 2-7). Figure 2-4 shows



(2-7)

the X-ray structure of *trans*-$RuCl_2$((*R*,*R*)-Me-DUPHOS)((*R*,*R*)-DPEN) (**5**) obtained by this procedure. Incidentally, this was only the third reported X-ray structure for a

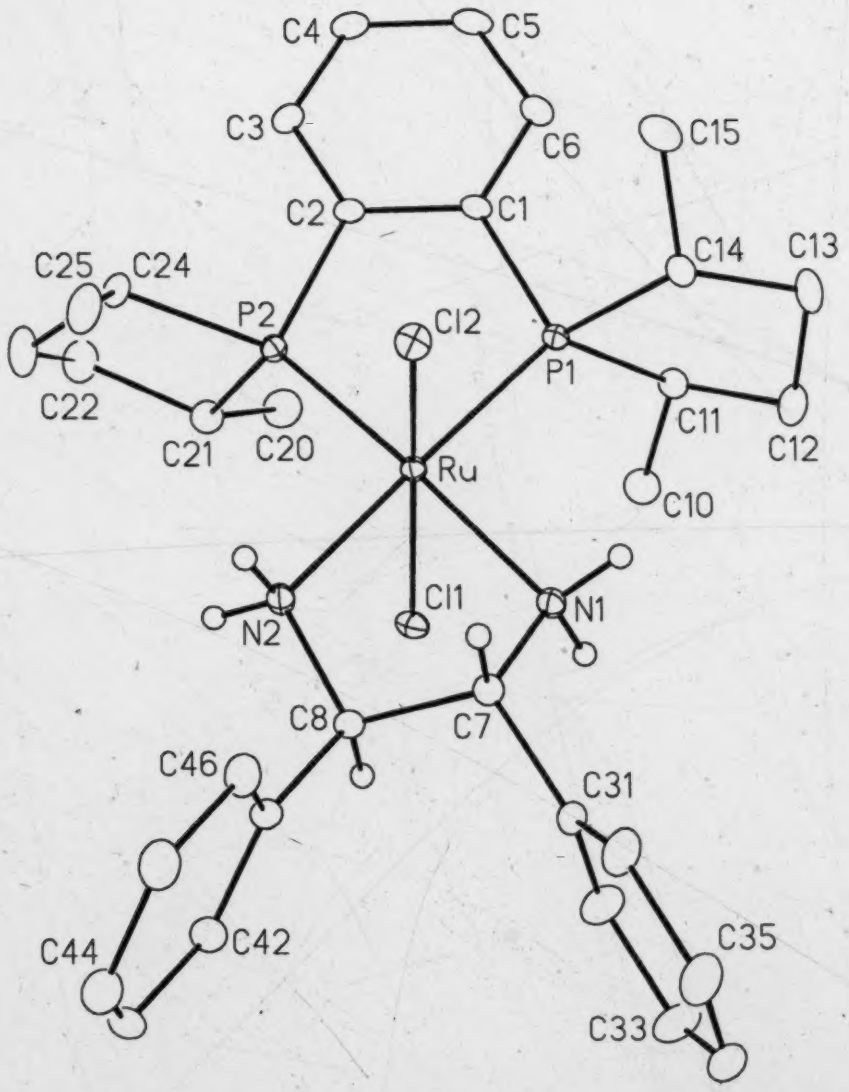


Figure 2-4. Perspective view of **5**•CH_2Cl_2 molecule showing the atom numbering scheme. The DPEN backbone hydrogen atoms are shown with arbitrarily small thermal parameters. All other hydrogens are not shown.

Table 2-3. Selected Interatomic Distances (Å) and Angles (deg) for 5•CH_2Cl_2

Ru–Cl1	2.4127(6)	P2–C24	1.878(3)
Ru–Cl2	2.4257(7)	C10–C11	1.521(4)
Ru–P1	2.2530(6)	C13–C14	1.542(4)
Ru–P2	2.2540(6)	N1–C7	1.496(3)
Ru–N1	2.1812(19)	N2–C8	1.486(3)
Ru–N2	2.1881(19)	C1–C2	1.395(4)
P1–C1	1.842(2)	C1–C6	1.406(3)
P1–C11	1.870(3)	C7–C8	1.538(3)
P1–C14	1.890(3)	C7–C31	1.5510(3)
P2–C2	1.852(2)	C20–C21	1.521(4)
P2–C21	1.870(3)	C21–C22	1.542(4)
Cl1–Ru–Cl2	165.97(2)	P1–Ru–N1	96.94(5)
Cl1–Ru–P1	100.37(2)	P1–Ru–N2	172.61(6)
Cl1–Ru–P2	93.15(2)	P2–Ru–N1	175.82(6)
Cl1–Ru–N1	82.87(6)	P2–Ru–N2	99.88(5)
Cl1–Ru–N2	85.01(6)	N1–Ru–N2	78.58(7)
Cl2–Ru–P1	90.14(2)	Ru–P1–C1	110.28(8)
Cl2–Ru–P2	97.04(2)	Ru–P1–C11	125.49(9)
Cl2–Ru–N1	86.69(6)	Ru–P1–C14	114.37(9)
Cl2–Ru–N2	83.77(6)	Ru–N1–C7	111.68(14)
P1–Ru–P2	84.99(2)	Ru–N2–C8	110.78(14)

ruthenium-DUPHOS complex.[34] The first two X-ray structures for such compounds were reported simultaneously by Morris *et al.*[35] for the complexes *trans*-[RuH(N_2)(Me-DUPHOS)$_2$]$^+$ (**5a**) and *trans*-[RuH(η^2-H_2)(Me-DUPHOS)$_2$]$^+$(**5b**). The geometry around the ruthenium atom in **5a** or **5b** is a distorted octahedral in which the metal atom and the four phosphorus atoms (two from each diphosphine) are in the same plane. The hydride ligand is above or below this plane and in a mutually *trans* position to either N_2 (**5a**) or η^2-H_2 (**5b**). The geometry around the Ru atom in **5** is also a distorted octahedral with the two chelating ligands forming the main plane of the complex and the two Cl^- ligands placed on either side of the plane as shown in figure 2-4. A comparison of the Ru-P bond lengths in **5** (av. 2.2535Å) to those of **5a** (av. 2.354 Å) or **5b** (2.365 Å) show that the bond lengths in **5** are approximately 0.1 Å shorter. The longer bonds in **5a** and **5b** could be rationalized by the fact that the phosphine groups are mutually *trans* in these compounds. Phosphines are known to have a large *trans* influence[36] and as such a mutually *trans* disposition of these groups results in net lengthening of the Ru-P bond. The P-Ru-P angle obtained for **5** (84.99°) is comparable to those obtained for **5a** (av. 83.16°) and **5b** (av. 83.1°). Some selected bond angles and distances for **5** are shown in Table 2-3.

trans-$RuCl_2$((*S*,*S*)-CHIRAPHOS)Py_2 (**3**) and *trans*-$RuCl_2$((*S*,*S*)-SKEWPHOS)Py_2 (**9**) were also reacted with (*S*,*S*)-DPEN to generate the diastereomers $RuCl_2$((*S*,*S*)-CHIRAPHOS)((*S*,*S*)-DPEN) (**6**) and $RuCl_2$((*S*,*S*)-SKEWPHOS)((*S*,*S*)-DPEN) (**7**). Although the diastereomers containing (*S*,*S*)-DPEN with the other diphosphine ligands were not prepared, there is no reason to assume they will not form according to equation 2-7. The ^{31}P NMR signals of **7** coalesce into a broad resonance at 40 °C. The signals appear as two sharp doublets at approximately -30 °C, however, suggesting that the compound exists in the *trans*- geometry with the chair conformation of the SKEWPHOS ligand preferred at low temperature.[37] Further investigations into the conformations of these SKEWPHOS-diamine complexes are in progress. As reported

by Noyori *et al.* when they developed them, such compounds are remarkably active catalysts for hydrogenations of aryl-alkyl ketones in *iso*-propanol solution in the presence of base.[20,38] Table 2-4 shows some selected results obtained for hydrogenation of 1'- acetonapthone using *trans*-$RuCl_2$((*R*)-BINAP)((*R*,*R*)-DPEN) (**8**) as catalyst and for hydrogenation of acetophenone using **5** and **7** as catalysts (using KO^{t}Bu as base) under conditions developed by Noyori *et al.*[20,38] It was found that compound **5**, though active, was not very selective for the hydrogenation of aryl-alkyl ketones giving only 15 % ee for the hydrogenation of acetophenone. However, recently compound **5** was shown to be highly enantioselective for the hydrogenation of the imine *N*-(phenylethylidene)aniline which proceeds in 85 % ee (*R*).[39] Interestingly, the dipyridine complexes were also active catalysts for the hydrogenation of acetophenone under these conditions. For example *trans*-$RuCl_2$((*S*,*S*)-SKEWPHOS)Py_2 (**9**) catalyzes the hydrogenation of acetophenone in 48 % ee (Table 2-4).

King *et al.* reported that addition of HCl(aq.) or other acids (~ 2 equivalents per Ru) to $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ causes dramatic rate enhancements for hydrogenations of β-keto esters and related substrates,[40] while retaining the high ee values reported previously by Noyori *et al.*[41] In our work, it was found that addition of 4 equivalents of aqueous HBF_4 (per Ru) to methanolic solutions of *trans*-$RuCl_2$(P-P*)Py_2 reproducibly caused an even greater enhancement in activity than addition of HCl (aq.). Catalysts that were inactive using HCl(aq.) were active using HBF_4(aq.). Aqueous HBF_4 was used previously by Takaya *et al.* to enhance the ee for hydrogenation of α-keto esters but still under 100 kg·cm^{-2} hydrogen pressure using $[RuX(\eta^6\text{-arene})(P\text{-}P^*)]^+$ as catalyst precursor.[32(f)] Our conditions for the hydrogenation of methyl acetoacetate were 60 °C, 0.1 % Ru, 0.4 % HBF_4(aq.), 3.7 atm H_2, 24 h. Table 2-4 shows the results obtained using the catalyst *trans*-$RuCl_2$((*R*)-BINAP)Py_2 (**2**)) for hydrogenation of methyl acetoacetate. We note that the use of (**2**)/HBF_4(aq.) produced

the same ee as use of (**2**)/HCl(aq.) for hydrogenation of this substrate, implying that the added chloride is not involved in the catalytic cycle.

Table 2-4. Representative Hydrogenations

Substrate	Catalyst	S/C[c]	Conversion %	ee %
Methyl acetoacetate	**2**/HCl(aq.)[a]	1000	100	99.9 (*R*)
Methyl acetoacetate	**2**/HBF_4(aq.)[a]	1000	100	99.9(*R*)
MAC	**2**/HBF_4(aq.)[a]	100	100	99(*R*)
MAC	**2**/HCl(aq.)[a]	100	100	99(*R*)
Tiglic acid	**2**[a]	100	100	91(*R*)
Tiglic acid	**10**/Et_3N[a]	100	100	82(*R*)
1'-Acetonaphthone	**8**[b]	500	95	82(*S*)
Acetophenone	**7**[b]	500	100	84(*R*)
Acetophenone	**5**[b]	500	100	15(*S*)
Acetophenone	**9**[b]	500	100	48(*R*)

[a]Hydrogenations done in methanol at 60°C under 3.7 atm. dihydrogen for 24h.

[b]Done in *iso*-propanol in presence of 4 equiv. of KO^tBu per Ru at 60°C, 3.7 atm for 24 h except for catalyst **7** which was done at r.t. under 2 atm. dihydrogen for 48h. [c]Substrate/Catalyst

It is interesting that addition of $HBF_4 \cdot OEt_2$ (2 equiv.) to methylene chloride-d_2 solutions of *trans*-$RuCl_2$((*R*)-BINAP)Py_2 produced, in near quantitative NMR yield, the same (as yet unidentified) species as the one reported by King *et al.*[40b] upon addition of methanesulfonic acid to methylene chloride solutions of $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$. Further investigations into the nature of this species are in progress.

These systems can also be used to hydrogenate olefins. (*Z*)-Methyl α-acetamidocinnamate (MAC) and tiglic acid were used as examples. Hydrogenation of MAC proceeded well using the *trans*-$RuCl_2$(P-P*)Py_2/HBF_4(aq.) system. Table 2-4 shows the result obtained using **2**/HBF_4(aq.) and using **2**/HCl(aq.)). It was previously reported that the hydrogenation of MAC using "$RuBr_2$(*R*)-BINAP" proceeds in 85 % ee (*R*) under ~ 98 atm of H_2.[42] Tiglic acid is hydrogenated without addition of HBF_4(aq). Instead, the hydrogenation either required no additive for promotion (e.g. using **2** as catalyst, Table 2-4), or it was promoted by addition of one equivalent of triethylamine per substrate (e.g. using *trans*-$RuCl_2$(*R*,*R*)-Me-DUPHOS)Py_2 (**10**), Table 2-4). Such enhancements in rate for hydrogenation of olefinic carboxylic acids by added amine are well-known in asymmetric catalytic hydrogenation.[1] The ee using **2** for hydrogenation of tiglic acid was identical to that reported by Noyori, *et al.*, using $Ru(O_2CCH_3)_2$((*R*)-BINAP) as catalyst.[43]

It was found convenient to carry out several (up to 8) hydrogenations at once in an autoclave (at 3.7 atm) by strapping several test tubes (each fitted with a magnetic stirbar and a rubber septum pierced with a large-bore syringe needle) together with an elastic band. A control experiment showed that when the reactions were magnetically stirred, as rapidly as possible, the rates and ee values for hydrogenations of methyl acetoacetate using **2**/HBF_4(aq.) as catalyst were the same as when carried out individually in a glass pressure reactor or together with other hydrogenations in an autoclave. Such control experiments are recommended to confirm the results obtained from several hydrogenations done at once as described here.

Conclusions

The previously reported discoveries and use of "$Ru(P\text{-}P^*)X_2$"[1a,b,17] and *trans*-$RuCl_2(P\text{-}P^*)(N\text{-}N^*)$[20] represent milestones in the development of enantioselective catalytic hydrogenation. A more versatile route to well-defined Ru(II) catalyst precursor complexes containing chiral diphosphine ligands has been presented. These complexes are obtained in yields that are greater than 85 % on a 1 g scale. Protocols for carrying out hydrogenations with these complexes under mild conditions have been described in this work. In these contexts, the importance of this work is not as much the ee values reported in Table 2-4, but the reactivities and methodologies used to obtain them. Although it cannot be predicted if compound **1** will be reactive towards all chiral diphosphine ligands, use of **1** will complement the previously reported syntheses of ruthenium complexes with chiral diphosphine ligands when evaluating a new chiral ligand or screening a variety of ligands for hydrogenation of a particular substrate. Ketoesters, non acidic olefins, and related substrates are hydrogenated using *trans*-$RuCl_2(P\text{-}P^*)Py_2/HBF_4$(aq.), α,β- or β,γ- unsaturated carboxylic acids are hydrogenated using *trans*-$RuCl_2(P\text{-}P^*)Py_2/NEt_3$, and unsubstituted ketones are hydrogenated using *trans*-$RuCl_2(P\text{-}P^*)(N\text{-}N^*)$/base (as described by Noyori *et al*).[20,43]

Experimental Section

Instrumentation. All ^{1}H and ^{31}P NMR spectra were measured on a Bruker AM-400 NMR spectrometer operating at 400.13 MHz and 161.97 MHz respectively or on a Bruker AM-200 NMR spectrometer operating at 200.13 MHz and 80.02 MHz respectively. ^{1}H NMR chemical shifts are reported in parts per million (δ) relative to tetramethylsilane using the solvent as an internal reference. ^{31}P NMR chemical shifts are reported in parts per million (δ) relative to an 85 % H_3PO_4 external reference. Microanalysis were performed at the University of Alberta Microanalysis Laboratory. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm (sodium D line) using 1.0 dm cells. Gas chromatography (GC) was performed on a Chiraldex® Gamma-Cyclodextrin Trifluoracetyl (GTA) column (30m x 0.25mm) or a Supelco β-Dex 120 column (β-Dex) (30m x 0.25 mm) fitted to a Hewlett Packard 5980A gas chromatograph with a Hewlett Packard 3392A integrator.

Reagents and Solvents. The solvents and reagents *n*-hexane (K, Ph_2CO), methylene chloride (CaH_2), tetrahydrofuran (K, Ph_2CO), diethyl ether (K, Ph_2CO), methanol ($Mg(OMe)_2$), *iso*- propanol ($Mg(O^iPr)_2$), and pyridine (CaH_2) were distilled from drying agents under argon. The argon and dinitrogen gases were passed through a bed of Drierite drying agent. Dihydrogen gas (Praxair, 99.99%) was passed through an Alltech Oxy-trap to remove trace amounts of oxygen. The diphosphine ligands (*R*)-BINAP, (*S*,*S*)-CHIRAPHOS, (*S*,*S*)-SKEWPHOS, (*R*,*R*)-NORPHOS, or (*R*,*R*)-Me-DUPHOS were used as received from Strem Chemicals Inc. Racemic 1-phenylethanol, methyl 3-hydroxybutyrate, 2-methylbutyric acid, as well as (*R*)-1-phenylethanol, (*S*)-methyl 3-hydroxybutyrate, (*S*)-2-methylbutyric acid, (*R*,*R*)- and (*S*,*S*)-DPEN were used as received from Aldrich Chemical Co., Inc. (*S*)-*N*-acetyl-L-phenylalanine methyl ester

was used as received from Serva. HBF_4(aq.), 48 - 50 % solution, purified grade, was used as received from Fisher Scientific Co. Unless stated otherwise, all other reagents were obtained from the Aldrich Chemical Co., Inc., of which the liquids were distilled before use. (*Z*)-Methyl α-acetamidocinnamate[43] and $[RuCl_2(NBD)]_n$[27] were prepared using published procedures.

General Procedures. Unless stated otherwise, all manipulations were carried out in oven-dried glassware using standard air-sensitive techniques. Esterifications using diazomethane[45] and conversion of alcohol hydrogenation products or authentic samples to their trifluoroacetate derivatives were carried out using literature procedures.[46]

***trans*-$RuCl_2(NBD)Py_2$ (1).** Thoroughly ground $[RuCl_2(NBD)]_n$ (0.794 g, 3.01 mmol) was rapidly stirred in pyridine (30 mL) for one week at room temperature under an atmosphere of dinitrogen. The mixture changed from a brown to greenish-yellow suspension during this time. The pyridine was removed under vacuum to give a greenish-yellow solid. The solid was exhaustively extracted with portions of hot ethyl acetate in air until little or no solid remained. Each portion of ethyl acetate was passed through a 2 x 30 cm column of neutral alumina in air. The resulting golden-amber solution (~ 250 mL) was pumped down on a rotary evaporator to yield 1.13 g of a yellow powder. Recrystallization from dichloromethane/hexanes under dinitrogen forms 1.08 g (85 % yield) of *trans*-$RuCl_2(NBD)Py_2$ as large dark-orange crystals. ^1H NMR: (200 MHz, CD_2Cl_2): δ 1.55 (br s, 2H C*H*$_2$), 4.05 (br s, 2H, bridgehead C*H*), 4.85 (m, 4H, olefin), 7.25 (br t, J = 11.9 Hz, 4H), 7.7 (br t, J = 11.9 Hz, 2H), 8.54 (br d, J = 12.0 Hz, 4H).

General Preparation of *trans*-$RuCl_2$(P-P*)Py_2. *trans*-$RuCl_2$(NBD)Py_2 (42.2 mg, 0.100 mmol) and the diphosphine ligand (0.100 mmol) were dissolved in dichloromethane (5 mL) under an atmosphere of dinitrogen and stirred at room temperature for 12 h. The solvent was removed under vacuum and the resulting yellow-amber powders recrystallized from dichloromethane/hexanes to yield the products typically as amber crystals in > 85 % yield.

***trans*-$RuCl_2$((*R*)-BINAP)Py_2 (2).** ^{31}P NMR (162 MHz, CD_2Cl_2): δ 40.87 (s) ^{1}H NMR (400 MHz,CD_2Cl_2): δ 6.30 (d, J = 9 Hz, 2H), δ 6.4-7.0 (m, 18H, Ar), 7.15 (t, J = 7.2 Hz, 2H), 7.28 (m, 2H), 7.55 (d, J = 9 Hz, 2H), 7.66 (m, 6H), 7.96 (br s, 4H), 8.10 (m, 2H)), 9.18 (br, 4H). Anal. Calcd for $C_{54}H_{42}Cl_2N_2P_2Ru \bullet CH_2Cl_2$: C, 60.00; H , 4.11; N, 2.50. Found: C, 60.16; H, 4.00; N, 2.50.

***trans*-$RuCl_2$((*S,S*)-CHIRAPHOS)Py_2 (3).** ^{31}P NMR (81 MHz, CD_2Cl_2): δ 74.29 (s). ^{1}H NMR (200 MHz, CD_2Cl_2): δ 0.99 (d, J = 6 Hz, 6H, CH_3); 2.91 (m, 2H, *CH*(Me)), 7.61 (br t, J = 8.4 Hz, 4H), 7.2-7.7 (m, 20H), 8.70 (d, J = 6 Hz, 4H). Anal. Calcd for $C_{38}H_{38}Cl_2N_2P_2Ru$: C, 60.32; H, 5.06; N, 3.70. Found: C, 60.24; H, 5.04; N, 3.65.

***trans*-$RuCl_2$((*R,R*)-Me-DUPHOS)Py_2 (10).** ^{31}P NMR (81 MHz, CD_2Cl_2): δ 89.97 (s). ^{1}H NMR (200 MHz, CD_2Cl_2): δ 0.77-0.99 (m, 12 H, CH_3), 1.31 (m, 2H), 1.64 (m, 2H), 2.18 (m, 4H), 2.85 (m, 4H), 7.27 (t, J = 7.5 Hz, 4H), 7.45 (m, 2H), 7.66-7.8 (m, 4H), 9.41 (m, 4H). Anal. Calcd for $C_{28}H_{38}Cl_2N_2P_2Ru$: C, 52.83; H, 6.02; N, 4.38. Found: C, 52.77; H, 6.32; N, 4.38.

***trans*-$RuCl_2$((*R,R*)-NORPHOS)Py_2 (4)** ^{31}P NMR (81 MHz, CD_2Cl_2): δ 33.95 (d, J_{PP} = 29 Hz, 1P), 35.24 (d, J_{PP} = 29 Hz, 1H). ^{1}H NMR (200 MHz, CD_2Cl_2): δ 0.55 (d, J = 8 Hz, 1H), 1.39 (d, J = 8 Hz, 1H), 2.68 (br s, 1H), 3.0-3.3 (m, 2H), 3.6 (br t, J = 18 Hz, 1H), 4.85 (m, 1H, olefin), 6.26 (m, 1H, olefin), 6.9-7.7 (m, 22H, Ar), 8.06 (t, J = 9 Hz,

2H), 8.26 (t, J = 9 Hz, 2H), 9.00 (m, 4H). Anal. Calcd for $C_{41}H_{38}Cl_2N_2P_2Ru$: C, 62.12; H, 4.83; N, 3.53. Found: C, 62.43; H, 4.65; N, 3.71.

***trans*-RuCl$_2$((*S*,*S*)-SKEWPHOS)Py$_2$ (9).** ^{31}P NMR (162 MHz, CD_2Cl_2): δ 50.42 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.04 (br s, 6H, C*H*$_3$), 2.08 (br t, J = 20.4 Hz, 2H), 3.37 (br s, 2H), 6.81 (br s, 4H), 6.91 (t, J = 9.6 Hz, 4H), 7.17 (t, J = 9.6 Hz, 2H), 7.24 (m, 4H), 7.33 (m, 8H), 7.53 (br s, 4H), 9.01 (br s, 4H). Anal. Calcd for $C_{39}H_{40}Cl_2N_2P_2Ru$: C, 60.78; H, 5.23; N, 3.39. Found: C, 61.17; H, 5.27; N, 3.39.

General Preparation of *trans*-RuCl$_2$(P-P*)(N-N*). *trans*-RuCl$_2$(P-P*)Py$_2$ (0.100 mmol) and (*R*,*R*)-DPEN (21.2 mg, 0.100 mmol) are dissolved in dichloromethane (5 mL) under an atmosphere of dinitrogen and stirred at room temperature for 2 h. The solvent was removed under vacuum and the resulting yellow-amber powders were recrystallized from dichloromethane/hexanes to yield the products typically as amber crystals in > 85 % yield.

***trans*-RuCl$_2$((*R*,*R*)-Me-DUPHOS)((*R*,*R*)-DPEN (5).** ^{31}P NMR (81 MHz, CD_2Cl_2): δ 92.51 (s). ^{1}H NMR (200 MHz, CD_2Cl_2): δ 0.69 (app dd, J = 13.8, 8.4 Hz, 6H, C*H*$_3$), 1.38 (app dd, J = 13.8, 8.4 Hz, 6H, C*H*$_3$), 1.66 (m, 4H), 2.25 (m, 4H), 2.84 (m, 4H), 4.25 (br s, 4H, dpen), 4.75 (m, 2H, dpen), 7.28 (m, 10H, Ar, dpen), 7.48 (m, 2H, Ar, DUPHOS), 7.78 (m, 2H, Ar, DUPHOS). Anal. Calcd for $C_{32}H_{44}Cl_2N_2P_2Ru \bullet CH_2Cl_2$: C, 51.11; H, 5.91; N, 3.55. Found: C, 50.93; H, 5.93; N, 3.56.

***trans*-RuCl$_2$((*S*,*S*)-CHIRAPHOS)((*S*,*S*)-DPEN) (6).** ^{31}P NMR (162 MHz, CD_2Cl_2): δ 78.73 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.99 (m, 6H, C*H*$_3$), 2.65 (br s, 2H, C*H*(Me)), 3.60 (br s, 2H), 4.05 (m, 2H), 4.54 (m, 2H), 7.0-7.51 (m, 30H, Ar). Anal. Calcd for $C_{42}H_{44}Cl_2N_2P_2Ru$: C, 62.22; H, 5.47; N, 3.46. Found: C, 62.11; H, 5.46; N, 3.94.

***trans*-RuCl$_2$((*S*,*S*)-CHIRAPHOS)((*R*,*R*)-DPEN).** ^{31}P NMR (162 MHz, CD_2Cl_2): δ 78.34 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.14 (app dd, J = 12, 6.5 Hz, 6H, C*H*$_3$), 2.64

(br s, 2H, C*H*(Me)), 3.64 (br d, H = 9.7 Hz, 2H), 4.03 (br s, 2H), 4.25 (d, J = 12 Hz, 2H), 7.0-7.7 (m, 30H, Ar).

***trans*-RuCl$_2$((*S*,*S*)-SKEWPHOS)((*S*,*S*)-DPEN) (7).** ^{31}P NMR (162 MHz, 25 °C, CD_2Cl_2): δ 54 (v br). ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 1.10 (br s, 6H, CH_3), 2.03 (br app t, J = 20.4 Hz, 2H), 2.6-3.7 (v br, 2H), 3.22 (br s, 2H), 3.82 (br s, 2H), 4.34 (br s, 2H), 7.0-7.8 (m, 30H, Ar). ^{31}P NMR (162 MHz, -60 °C, CD_2Cl_2): δ 59.68 (d, J = 47.43 Hz, 1P), 46.82 (d, J= 47.43 Hz, 1P). ^{1}H NMR (400 MHz, -60 °C, CD_2Cl_2): δ 0.85 (dd, J = 11, 6.6 Hz, 3H, CH_3), 1.12 (dd, J = 14. 7 Hz, 3H, CH_3), 1.81 (dq, J = 31, 14 Hz, 1H C*H*(Me)), 2.01 (br s, 1H), 2.07 (q, J = 13 Hz, 1H), 3.02 (br s, 1H), 3.18 (br s, 1H), 3.86 (m, 2H), 4.05 (m, 2H), 4.5 (br t, J = 13 Hz, 1H), 6.62-7.8 (m, 30H, Ar). Anal. Calcd for $C_{43}H_{46}Cl_2N_2P_2Ru$: C, 62.62; H, 5.59; N, 3.40. Found: C, 62.03; H, 5.55; N, 4.05.

***trans*-RuCl$_2$((*S*,*S*)-SKEWPHOS)((*R*,*R*)-DPEN).** ^{31}P NMR (81 MHz, 25 °C, CD_2Cl_2): δ 55 (v br). ^{1}H NMR (200 MHz, 25 °C, CD_2Cl_2): δ 1.04 (app d, J = 7 Hz, 6H, CH_3), 1.12 (d, J = 7.4 Hz, 3H, CH_3), 1.97 (br t, J = 21.8 Hz, 2H), 2.6-3.3 (v br, 2H), 3.9 (m, 2H), 4.34 (m, 2H), 6.9-7.8 (m, 30H, Ar). Anal. Calcd for $C_{43}H_{46}Cl_2N_2P_2Ru$: C, 62.62; H, 5.59; N, 3.40. Found : C, 61.67; H, 5.62; N, 3.74.

***trans*-RuCl$_2$((*R*)-BINAP)((*R*,*R*)-DPEN) (8).** ^{31}P NMR (162 MHz, CD_2Cl_2): δ 46.37 (s). ^{1}H NMR (400 MHz, CD_2Cl_2): δ 2.89 (br s, 2H), 3.25 (br s, 2H), 4.25 (br s, 2H), 6.19 (m, 2H), 6.51 (br s, 6H), 6.64 (m, 2H) 6.84 (br s, 4H), 7.0-7.4 (m, 14H), 7.45-8.08 (m, 2H), 8.24 (s, 2H). This compound was prepared previously by Noyori *et al.*[2c] Anal. Calcd for $C_{58}H_{48}Cl_2N_2Ru \bullet CH_2Cl_2$: C, 64.90; H, 4.62; N, 2.61. Found: C, 64.57; H, 4.84, N, 2.78.

***trans*-RuCl$_2$((*R*,*R*)-NORPHOS)((*R*,*R*)-DPEN).** ^{31}P NMR (81 MHz, CD_2Cl_2): δ 43.8 (AB, J = 33.3 Hz), δ 44.1 (AB, J = 33.3 Hz) ^{1}H NMR (200 MHz, CD_2Cl_2): δ 0.73 (br d, J = 9 Hz, 1H, CH_2), 1.57 (br d, J = 9 Hz, 1H, CH_2), 2.81 (br s, 1H), 2.97 (br t, J = 12.5 Hz, 1H), 3.13 (br s, 1H), 3.3-3.8 (m, 3H), 4.5 (m, 4H), 5.21 (dd, J = 5.5, 3.0 Hz,

1H, olefin), 6.24 (dd, J = 5.5, 3.3 Hz, 1H, olefin), 7.5-7.0 (m, 26H, Ar), 7.98 (br t, J = 16.3 Hz, 2H, dpen), 8.12 (br t, J = 15.5 Hz, 2H, dpen). Anal. Calcd for $C_{45}H_{44}Cl_2N_2P_2Ru$: C, 63.83; H, 5.24; N, 3.31. Found: C, 61.27; H, 4.99; N, 3.89.

General Procedure for Hydrogenations Carried out With *trans*-$RuCl_2$(P-P*)Py_2 as Catalyst Precursor. The catalyst precursor (0.0152 mmol) was weighed into a glass pressure reactor containing a magnetic stirbar. The reactor was then fitted with a rubber septum and flushed with argon gas. Dry, distilled MeOH (3.4 mL) was added to the vessel using a syringe forming a yellow-amber suspension. HBF_4(aq) (48 %, 8.0 μL 4 equiv.) or HCl(aq) (30.4μL of 2M solution) or Et_3N (15.2 mmol) are then added with a gas-tight syringe. Titrated solutions of HBF_4(aq) (2 M) can be used in place of the 48 % solution, if desired. The catalyst precursor dissolved forming a yellow-amber solution on stirring for a few minutes after addition of the acid. The argon-saturated (bubbled 20 min) substrate (15.2 mmol) was then introduced using a syringe. Solid substrates were added as a concentrated solution in MeOH, or they were weighed in the pressure reactor with the catalyst if required. Dihydrogen gas was then bubbled through the solution with rapid stirring for 10 min. The septum was replaced with the pressure lid of the reactor, and the system pressurized (40 psi gauge pressure) and vented three times with dihydrogen gas before finally being pressurized to 40 psi and placed in a 60 °C oil bath with rapid stirring for 24 h. The solutions tend to turn a red-amber colour during the hydrogenations. The mixture was then cooled, flushed with dinitrogen, and the methanol removed on a rotovap. The catalyst residues were removed from the products by dissolving the product residue in diethyl ether and passing the mixture through a Florisil plug. The yields and ee values are shown in Table 2-4. Several of these hydrogenations can be carried out simultaneously by using test tubes as reaction vessels fitted with rubber septa and containing magnetic stirring bars. After charging the test tubes with catalyst, acid, and substrate as described above, their septa were pierced with large-bore syringe needles in a glovebag under an

atmosphere of dinitrogen. The test tubes were placed in a steel autoclave, the autoclave was sealed, and then pressurized with dihydrogen gas (40 psi gauge pressure) and vented six times with rapid magnetic stirring prior to beginning the hydrogenation.

General Procedure for Hydrogenations Carried out With *trans*-$RuCl_2$(P-P*)(N-N*). These reactions were set up using KO^{t}Bu (4 equiv. per Ru) as base in in 3.4 mL of ^{i}PrOH solvent as described previously by Noyori *et al.*[20] The reaction mixtures were pumped down on a rotovap and the product separated from the catalyst as described above.

Derivatization of Products and Determination of Absolute Configuration and ee. The products from the catalytic hydrogenations as well as authentic racemic and optically pure 1-phenylethanol and methyl 3-hydroxybutyrate were converted into their trifluoroacetates as described in the literature.[46] The ee values and absolute configurations of the hydrogenation products were determined by retention times and peak areas in gas chromatograms obtained using the GTA column. The products from the catalytic hydrogenations as well as authentic racemic and optically pure 2-methylbutyric acid were esterified using diazomethane using a literature procedure.[46] The ee value and absolute configuration of the hydrogenation products were determined by retention times and peak areas using the GTA column. The ee and absolute configuration of *N*-acetyl-L-phenylalanine methyl ester obtained from hydrogenation of MAC was obtained using authentic (*S*)-*N*-acetyl-L-phenylalanine methyl ester and the GTA column. The ee of the 1-(1-naphthyl)ethanol obtained from hydrogenation of 1'-acetonaphthone was obtained using the β-DEX column and by comparing the optical rotation to that reported in the literature.[17d] The retention times and GC conditions for the products using helium as carrier gas are as follows:

1-(1-Naphthyl)ethanol (TFA): t_R = 46.15 min, t_S = 44.01 min, temp. = 150°C, 8 psi head pressure.

1-Phenylethanol (TFA): t_R = 30.99 min, t_S = 32.70 min, temp. = 65°C, 8 psi head

pressure.

N-acetyl-L-phenylalanine methyl ester: t_R = 43.90 min, t_S = 42.07 min, temp. = 140°C, 24 psi head pressure.

Methyl 3-hydroxybutyrate (TFA): t_R = 10.92 min, t_S = 25.33 min, temp. = 80°C, 8 psi head pressure.

2-Methylbutyric acid (methyl ester): t_R = 7.99 min, t_S = 8.55 min, temp. = 60°C, 8 psi head pressure.

X-ray crystallography

***trans*-$RuCl_2(NBD)Py_2$ (1).** Crystals of **1** suitable for structure determination by X-ray diffraction were obtained by slow liquid-liquid diffusion of hexanes into a saturated solution of **1** in CH_2Cl_2 at r.t. Data collection, structure solution, and structure refinement for this and all other compounds reported in this chapter were performed by Dr. Robert McDonald, Faculty Service Officer, Structure Determination Laboratory, Department of Chemistry, University of Alberta. Final atomic coordinated and displacement parameters for these compounds can be obtained from the Structure Determination Laboratory, under the file codes; SHB 9803, SHB 9903, SHB 9808 and SHB 9906 for compounds **1**, **2**, **3** and **5** respectively. Table 2-1 shows the selected bond lengths and bond angles for compound **1**. Crystallographic experimental details are given in Table 2-5.

***trans*-$RuCl_2$((*R*)-BINAP)Py_2•2CH_2Cl_2 (2).** Crystals of **2** suitable for structure determination by X-ray diffraction were obtained by dissolving **2** in hot CH_2Cl_2 and allowing the hot solution to cool to r.t. Crystals formed as the hot solution cooled. See Table 2-2 for selected bond lengths and angles for this compound. Table 2-6 gives a summary of the crystal data, X-ray data collection and structure solution and refinement information for this compound.

***trans*-$RuCl_2$((*S*,*S*)-CHIRAPHOS)Py_2 (3).** Crystals of **3** were obtained in a similar manner to those of **1**. Crystal data, details of data collection and structure solution and refinement are outlined in table 2-7. Selected bond distances and angles are given in tables 2-2.

***trans*-$RuCl_2$((*R*,*R*)-Me-DUPHOS)((*R*,*R*)-DPEN (5).** Crystals of **5** were also obtained in like manner to those of **1**. Table 2-8 outlines the crystal data, details of data collection, and structure solution and refinement for **5**. Table 2-3 shows the selected bond lengths and bond angles for this compound.

Table 2-5. Crystallographic Experimental Details for 1

A. Crystal Data	
Formula	$C_{17}H_{18}Cl_2N_2Ru$
formula weight	422.30
crystal dimensions (mm)	0.24 × 0.24 × 0.20
crystal system	trigonal (hexagonal axes)
space group	$R\bar{3}$ (No. 148)
unit cell parameters[a]	
a (Å)	28.4376 (5)
c (Å)	10.8729 (6)
V (Å^3)	7614.9 (5)
Z	18
ρcalcd (g cm^{-3})	1.658
μ (mm^{-1})	10.36
B. Data Collection and Refinement Conditions	
Diffractometer	Siemens P4/RA[b]
radiation (λ [Å])	graphite-monochromated Cu Kα (1.54178)
temperature (°C)	–60
scan type	θ–2θ
data collection 2θ limit (deg)	115.0
total data collected	4577 ($-29 \le h \le 29$, $-31 \le k \le 30$, $-11 \le l \le 11$)[c]
independent reflections	2181
number of observed reflections (*NO*)	1938 [$F_o^2 \ge 2\sigma(F_o^2)$]
structure solution method	Direct methods (*SHELXS–86*[d])
refinement method	Full-matrix least-squares on F^2 (*SHELXL–93*[e])
absorption correction method	Semiempirical (Ψ scans)
range of transmission factors	0.8820–0.5707
data/restraints/parameters	2181 [$F_o^2 \ge -3\sigma(F_o^2)$] / 0 / 199
goodness-of-fit (*S*)[f]	1.083 [$F_o^2 \ge -3\sigma(F_o^2)$]
final R indices[g]	
$F_o^2 \ge 2\sigma(F_o^2)$	$R1 = 0.0389$, $wR2 = 0.0920$
All data	$R1 = 0.0448$, $wR2 = 0.0948$
largest difference peak and hole	0.469 and –0.941 e Å^{-3}

[a]Obtained from least-squares refinement of 42 reflections with $49.2° < 2\theta < 57.7°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Siemens.

[c]Data were collected from Friedel-opposite regions of reciprocal space with indices of the form $(+h\ -k\ -l)$ and $(-h\ +k\ +l)$. Because of the *R*-centering condition only reflections with $-h+k+l = 3n$ (n an integer) were collected.

[d]Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.

[e]Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993. Refinement on F_o^2 for all reflections (all of these having $F_o^2 \geq -3\sigma(F_o^2)$). Weighted *R*-factors wR_2 and all goodnesses of fit *S* are based on F_o^2; conventional *R*-factors R_1 are based on F_o, with F_o set to zero for negative F_o^2. The observed criterion of $F_o^2 > 2\sigma(F_o^2)$ is used only for calculating R_1, and is not relevant to the choice of reflections for refinement. *R*-factors based on F_o^2 are statistically about twice as large as those based on F_o, and *R*-factors based on ALL data will be even larger.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0478P)^2 + 25.4151P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2-6. Crystallographic and Experimental Details for 2•2CH_2Cl_2

A. Crystal Data	
formula	$C_{56}H_{46}Cl_6N_2P_2Ru$
formula weight	1122.66
crystal dimensions (mm)	0.14 × 0.13 × 0.12
crystal system	triclinic
space group	*P*1 (No. 1)
unit cell parameters[a]	
a (Å)	11.730 (2)
b (Å)	11.817 (2)
c (Å)	11.923 (2)
α (deg)	119.430 (3)
β (deg)	114.821 (3)
γ (deg)	93.939 (3)
V (Å^3)	1224.9 (4)
Z	1
ρcalcd (g cm^{-3})	1.522
μ (mm^{-1})	0.754
B. Data Collection and Refinement Conditions	
diffractometer	Bruker P4/RA/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ø rotations (0.3°) / ω scans (0.3°)(15 s exposures)
data collection 2θ limit (deg)	51.40
total data collected	8959 (-14 ≤ *h* ≤ 14, -14 ≤ *k* ≤ 14, -14 ≤ *l* ≤ 14)
independent reflections	8959
number of observations (*NO*)	7010 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–86*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–93*[d])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	0.9546–0.8780
data/restraints/parameters	8959 [$F_o^2 \geq -3\sigma(F_o^2)$] / 0 / 599
Flack absolute structure parameter[e]	-0.02 (7)
goodness-of-fit (*S*)[f]	1.048 [$F_o^2 \geq -3\sigma(F_o^2)$]
final *R* indices[g]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0877
wR_2 [$F_o^2 \geq -3\sigma(F_o^2)$]	0. 2671
largest difference peak and hole	3.894 and –1.392 e Å^{-3}

[a]Obtained from least-squares refinement of 4350 centered reflections.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.

[d]Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993. Refinement on F_o^2 for all reflections (all of these having $F_o^2 \geq -3\sigma(F_o^2)$). Weighted R-factors wR_2 and all goodnesses of fit S are based on F_o^2; conventional R-factors R_1 are based on F_o, with F_o set to zero for negative F_o^2. The observed criterion of $F_o^2 > 2\sigma(F_o^2)$ is used only for calculating R_1, and is not relevant to the choice of reflections for refinement. R-factors based on F_o^2 are statistically about twice as large as those based on F_o, and R-factors based on ALL data will be even larger.

[e]Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.1868P)^2]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2-7. Crystallographic Experimental Details for 3

A. Crystal Data	
formula	$C_{38}H_{38}Cl_2N_2P_2Ru$
formula weight	756.61
crystal dimensions (mm)	0.79 × 0.34 × 0.27
crystal system	hexagonal
space group	$P6_5$ (No.170)
unit cell parameters[a]	
a (Å)	11.5330 (6)
c (Å)	44.856 (3)
V (Å^3)	5167.0 (5)
Z	6
ρ_{calcd} (g cm^{-3})	1.459
μ (mm^{-1})	0.733
B. Data Collection and Refinement Conditions	
diffractometer	Siemens P4/RA[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–60
scan type	ω
data collection 2θ limit (deg)	50.0
total data collected	13258 ($-13 \le h \le 13$, $-13 \le k \le 13$, $-53 \le l \le 53$)[c]
independent reflections	6077
number of observations (NO)	5060 ($F_o^2 \ge 2\sigma(F_o^2)$)
structure solution method	direct methods/fragment search (DIRDIF–96[d])
refinement method	full-matrix least-squares on F^2 (SHELXL–93[e])
absorption correction method	(ψ scans)
range of transmission factors	0.9619–0.9010
data/restraints/parameters	6077 [$F_o^2 \ge -3\sigma(F_o^2)$] / 0 / 406
Flack absolute structure parameter[f]	0.02 (3)
goodness-of-fit (S)[g]	1.015 [$F_o^2 \ge -3\sigma(F_o^2)$]
final R indices[h]	
$F_o^2 > 2\sigma(F_o^2)$	$R_1 = 0.0408$, $wR_2 = 0.0755$
all data	$R_1 = 0.0572$, $wR_2 = 0.0820$
largest difference peak and hole	0.312 and –0.329 e Å^{-3}

[a] Obtained from least-squares refinement of 40 reflections with $21.3° < 2\theta < 24.3°$.

[b] Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Siemens.

[c] Data were collected with indices of the form $(+h -k +l)$ and $(-h +k -l)$.

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[f] Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration.

[g] $S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0303P)^2]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$).

[h] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2-8. Crystallographic and Experimental Details for 5•CH_2Cl_2

A. Crystal Data	
formula	$C_{33}H_{46}Cl_4N_2P_2Ru$
formula weight	775.53
crystal dimensions (mm)	0.18 × 0.18 × 0.10
crystal system	orthorhombic
space group	$P2_12_12_1$ (No. 19)
unit cell parameters[a]	
a (Å)	13.4843 (8)
b (Å)	13.8680 (9)
c (Å)	18.9519 (11)
V (Å^3)	3544.0 (4)
Z	4
ρ_{calcd} (g cm^{-3})	1.453
μ (mm^{-1})	0.860
B. Data Collection and Refinement Conditions	
diffractometer	Bruker P4/RA/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ø rotations (0.3°) / ω scans (0.3°) (30 s exposures)
data collection 2θ limit (deg)	51.50
total data collected	20802 (-16 ≤ h ≤ 16, -16 ≤ k ≤ 16, -22 ≤ l ≤ 23)
independent reflections	6736
number of observations (NO)	6226 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods (SHELXS–86[c])
refinement method	full-matrix least-squares on F^2 (SHELXL–93[d])
absorption correction method	SADABS
range of transmission factors	0.9076–0.7017
data/restraints/parameters	6736 [$F_o^2 \geq -3\sigma(F_o^2)$] / 0 / 379
Flack absolute structure parameter[e]	-0.03 (2)
goodness-of-fit (S)[f]	0.998 [$F_o^2 \geq -3\sigma(F_o^2)$]
final R indices[g]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0260
wR_2 [$F_o^2 \geq -3\sigma(F_o^2)$]	0.0556
largest difference peak and hole	0.342 and –0.282 e Å^{-3}

[a]Obtained from least-squares refinement of 6367 centered reflections.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.

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[e]Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0248P)^2]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

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Chapter 3†

Influence of Diamine ligands on the Rates and Selectivity of Ruthenium(II)-Diphosphine Catalyzed Hydrogenation of 1'-Acetonaphthone

Introduction

The hydrogenation of simple ketones (those without coordinating heteroatoms other than the carbonyl group) using homogeneous catalysis has been a challenging problem for synthetic chemists.[1] Some early examples of this type of hydrogenation using ruthenium complexes include: the hydrogenation of cyclohexanone using the cluster compound $H_4Ru_4(CO)_{10}(PPh_3)_2$,[2] the hydrogenation of cyclohexanone using the monomeric complex $[RuH_3(PPh_3)_3]^-$,[3] and the hydrogenation of acetophenone using the trinuclear complex $\{RuHCl(dppb)\}_3$.[4] These early catalyst systems proved effective for specific substrates but synthetically versatile catalyst systems were unknown until recently.

Noyori and co-workers[5] have discovered a ruthenium catalyst system that is versatile, highly active, and the most selective for enantioselective hydrogenation of

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A version of this chapter has been published.

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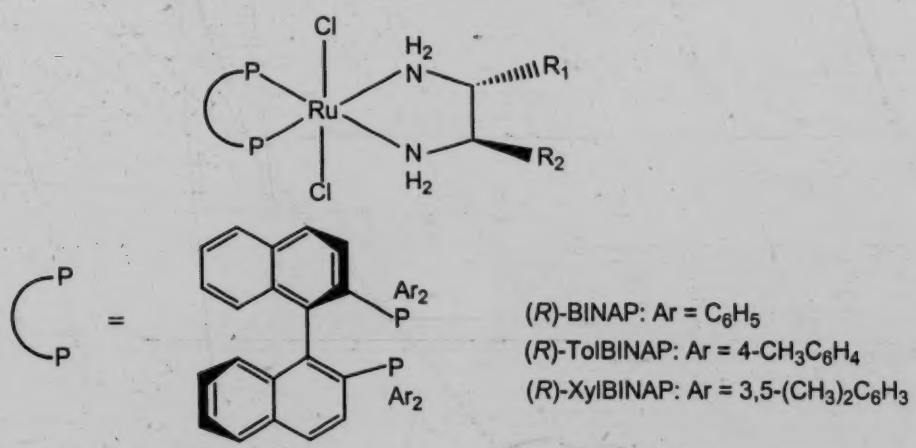
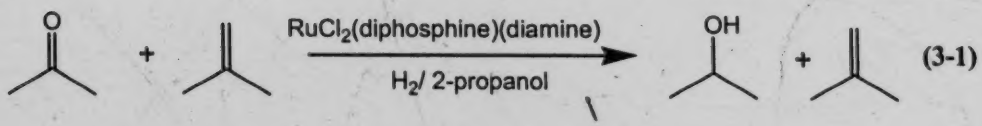
aryl-alkyl ketones. The catalyst system consists of diphosphine ruthenium(II) chloride (1,2-diamine) complexes (Scheme 3-1). This system has been the subject of a number of recent reports[1c,1d,5-10] and only pertinent aspects will be discussed here. The catalyst operates under mild conditions (usually 4-10 atm H_2 11-45 ^{0}C) and in the presence of alkali metal base using 2-propanol as solvent. The bases used in this system are alkali metal alkoxides with KO^{t}Bu, KO^{i}Pr and NaOiPr being the most common.[5] Alkali metal hydroxides, specifically KOH[5] has also been found to be effective. This catalyst system

Scheme 3-1. The Noyori catalyst system



has the highest activity for hydrogenation of aryl-alkyl ketones, achieving a TOF of 6700 h^{-1} in some cases.[5] Very small amounts of catalyst are often employed, with substrate: catalyst ratio = 2.4 million having been reported in a hydrogenation using this system.[7] These catalysts are known to be highly sensitive to minute quantities of acid impurities and substrates for hydrogenation must be carefully washed with KOH, otherwise the catalyst becomes inactive during reactions.[8] These catalysts are also the

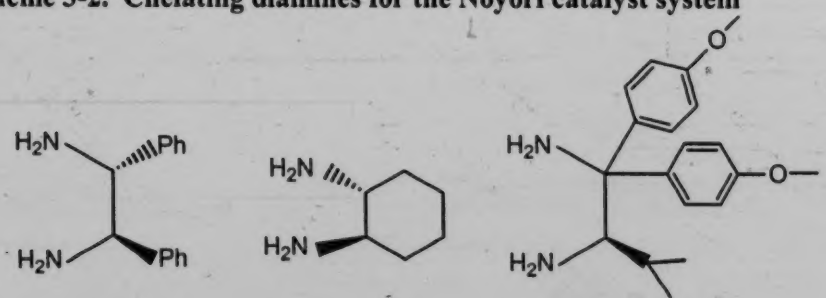
only known homogeneous transition metal catalysts that can effect selective hydrogenation (chemo-selective hydrogenation) of carbonyl groups over olefins[6] (equation 3-1). For high enantioselectivity, the diphosphine ligands used are



(3-1)

mostly BINAP and its derivatives.[1c] A variety of chiral chelating 1,2-diamines are also used, some examples are shown in Scheme 3-2.[5] It is believed that the major role of the diamine is to assist in hydrogen transfer to the carbonyl group of the ketone. The amine plays this role by hydrogen bonding to the oxygen atom of the carbonyl group. This hydrogen bonding to the oxygen atom withdraws electron density from the carbonyl

Scheme 3-2. Chelating diamines for the Noyori catalyst system



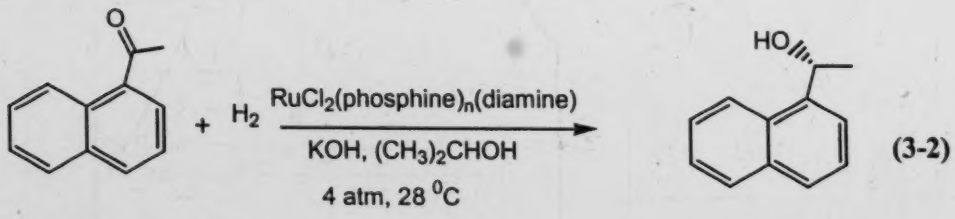
(a) (b) (c)

(a) = (*R*,*R*)-1,2-diphenylethylenediamine ((*R*,*R*)-DPEN)

(b) = (*R*,*R*)-cyclohexane-1,2-diamine

(c) = (*R*)-1,1-di-4-anisyl-2-isopropyl-1,2-ethylenediamine ((*R*)-DAIPEN)

carbon atom, activating it towards nucleophilic attack by the hydride ligand. Furthermore, hydrogen bonding prevents the formation of undesirable η^1-complexes



(3-2)

and at the same time positions the ketone for preferential hydride attack from the metal towards one enantiotopic face of the ketone. For these reasons, the chelating diamine must possess at least one primary or secondary amine that can hydrogen-bond to the carbonyl oxygen in order to facilitate simultaneous proton and hydride transfer.[1c] The stereo-directing role of the diamine can be seen from the data summarized in table 3-1, for the hydrogenation of 1'-acetonapthone according to the reaction in equation 3-2.[5] As can be seen from the table, the degree of enantioselectivity is dependant on the absolute configuration of both the diphosphine and the diamine. Replacement of (*S*,*S*)-DPEN with the (*R*,*R*)- enantiomer, results in reduction of enantioselection from 97 % ee to 14 % ee (entries 1 and 2). Use of achiral diamine results in decrease in enantioselectivity to 57 % ee (entry 3). Similarly, there is loss in enantioselectivity if an achiral phosphine is used (entry 4). Therefore matching the chiral diphosphine and diamine is required for high selectivity by these systems.

Morris *et al.*[9] have shown that the function of the alkali metal base in the $RuCl_2$(diphosphine)(diamine) hydrogenation system is to generate the active catalysts that are believed to be dihydride species *trans*-$Ru(H)_2$(diphosphine)(1,2-diamine).

Table 3-1. Dependance of Selectivity on Phosphine and Diamine for the Noyori Catalyst System.[5]

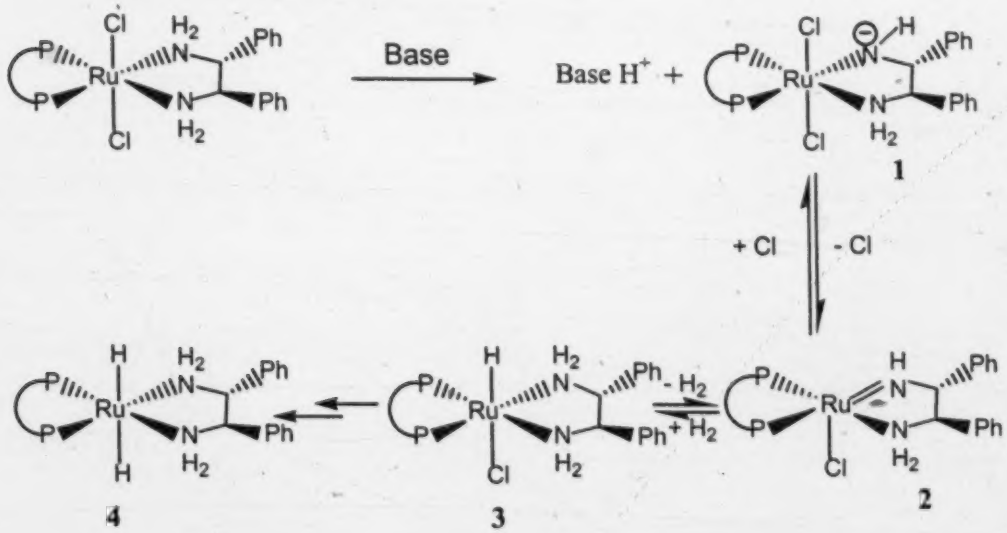
entry	Phosphine	Diamine	ee %
1	(*S*)-BINAP	(*S*,*S*)-DPEN	97
2	(*S*)-BINAP	(*R*,*R*)-DPEN	14
3	(*S*)-BINAP	$NH_2(CH_2)_2NH_2$	57
4	$P(C_6H_5)_3$	(S,S)-DPEN	75

The complexes Ru(H)Cl((*R*)-BINAP)((*R*,*R*)-DPEN)[9b] and $Ru(H)_2$((*R*)-BINAP)(tmen)[9c] have been isolated and characterized by X-ray crystallography. In benzene solution, or in neat substrate, the monohydride complex Ru(H)Cl((*R*)-BINAP)((*R*,*R*)-DPEN) was found to be inactive as a hydrogenation catalyst in absence of base. In the presence of base, this monohydride complex generated the dihydride complex $Ru(H)_2$((*R*)-BINAP)((*R*,*R*)-DPEN), as characterized by NMR. The dihydride was unstable and could not be isolated; however, it was used *in-situ* as a catalyst for the hydrogenation of simple ketones. It was also possible to use the isolated dihydride $Ru(H)_2$((*R*)-BINAP)(tmen) as a hydrogenation catalyst without adding any base to the reaction mixtures. The conclusions from these studies were that the actual catalysts for hydrogenation, at least in benzene or neat substrate, are the dihydride species of the type $Ru(H)_2$(diphosphine)(diamine).

The dihydrides are suspected[10] to be generated from the dichloride precursors by the dissociative conjugate base mechanism (Dcb).[11] As depicted in scheme 3-3, attack on the catalyst precursor by base is proposed to generate species **1** that readily dissociates the chloride ligand to form **2**, the latter can heterolytically

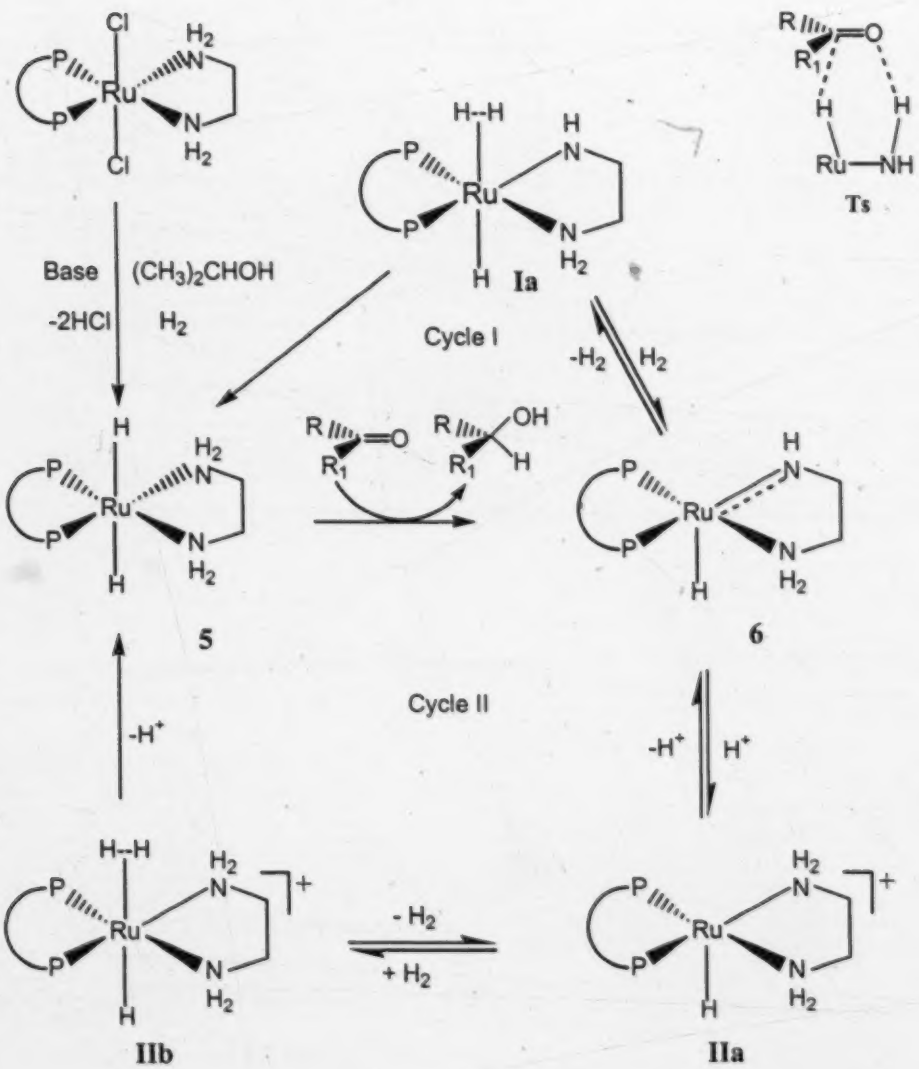
cleave dihydrogen to give the monohydride **3**. A repeat of the overall process would generate **4** that has been shown to be the actual catalyst in benzene or neat substrate.[9b] A point to be noted here is that the dihalide precursors are 18-electron

Scheme 3-3. Generation of dihydride species in the Noyori catalyst



species that have chelating diphosphine and diamine ligands (scheme 3-1) and are unlikely to undergo β-hydride elimination to form hydride species. A vacant coordination site is a requirement for β-elimination from transition metal complexes.[12] For the generation of hydrides from halide-containing 16-electron ruthenium complexes often used in transfer hydrogenation using 2-propanol as hydride source in presence of alkali metal bases, β-hydride elimination is the preferred pathway.[13,14] Bäckvall *et al.* have shown that the role of the added base to the complex $RuCl_2(PPh_3)_3$, used in ketone transfer hydrogenation, is to generate the active catalytic species $RuH_2(PPh_3)_3$.[14a,d]

Scheme 3-4. Morris/Noyori proposed mechanism for simple ketone hydrogenation[9d,10]



The mechanism proposed for this system has been termed as metal-ligand bifunctional catalysis by Noyori and co-workers.[1c,1d,10,15] It was first proposed by the Noyori group for a different hydrogen-transfer catalyst.[16] This mechanism has been the subject of a number of recent publications.[9d,9e,17] Noyori's proposed mechanism differs significantly from the classical ketone hydrogenation mechanism[18] in that the ketone group does not coordinate directly to the transition metal. As shown in scheme 3-4, two catalytic cycles are believed to operate depending on the reaction conditions.[10] The complexes **5** and **6** are common to both cycles. In aprotic solvents, kinetic data suggest that cycle I is the major pathway for the system.[9e,d] The reducing species **5** reacts with the ketone to form the 16-electron species **6**, which in turn reacts with H_2 to regenerate **5**, via the dihydrogen complex **Ia** to complete the cycle. In protic solvents (mainly 2-propanol) at low base concentrations cycle II is suspected to dominate.[10] In cycle II, the 16-electron species **6** is protonated by the solvent to form the cationic complex **IIa**. Reaction of **IIa** with H_2 gives **IIb** that undergoes deprotonation from the η^2-H_2 ligand to regenerate the dihydride **5**.

The reducing species **5** reacts with the ketone directly by a metal-ligand bifunctional mechanism[1c,1d,15] that proceeds via the six-membered transition state **Ts** in scheme 3-4. Delivery of a hydride from the Ru centre and a proton from NH_2 ligand takes place simultaneously, thereby forming the alcohol product directly without formation of a metal alkoxide. This mechanism is also believed to operate in the closely related ruthenium-catalyzed transfer hydrogenation of ketones using 2-propanol.[9d,9e,15,16,19,20,21]

Hartmann and Chen[17b] propose that the base plays a second important role in this mechanism in addition to generating the active catalyst species. They suggest that the base is a source of potassium ion that is essential for the high activity of this catalyst. The role of the potassium ion is to coordinate to the amido nitrogen of the intermediate **6** (scheme 3-4) and withdraw electron density from the amido ligand and hence from the ruthenium center. This withdrawal renders the ruthenium center sufficiently acidic to strongly bind and cleave H_2. Morris *et al.*,[9d] however did not observe any rate enhancement when KO^{t}Bu was added to ketone solution in benzene. For hydrogenations done in 2-propanol, Noyori *et al.*[10] reported that the addition of alkali metal cations increased the rate of catalysis in basic solutions, but decreased the rate in neutral solutions. The role of the alkali metal cation, if any, is not well understood in this mechanism at this stage. However, there are now Noyori-type catalyst systems that operate under base free conditions even in 2-propanol which may suggest that the alkali metal cation is not mandatory for the reaction to proceed.[8,9a,10]

We are interested in the Noyori-type catalyst system for three reasons. First, the versatile synthetic method developed in Chapter 2 for the preparation of $RuCl_2$(diphosphine)(diamine) complexes enabled us to make such compounds containing diphosphine ligands that, hitherto, had not been used in aryl-alkyl ketone hydrogenation. Secondly, any system that requires low loadings of catalyst to effect ketone or aldehyde hydrogenation, whether enantioselective or not, has potential for application in industry because it can replace the traditional cumbersome reductive systems based on hydride reagents such as $LiAlH_4$. Lastly, since these complexes are the most active for catalytic hydrogenation of ketones, it was of interest to compare

their rates to those of Py containing complexes, $RuCl_2$(diphosphine)Py_2, with a view of finding other possible auxilliary ligands that can substitute DPEN.

In this chapter, a number of catalyst precursors of the type $RuCl_2$(diphosphine) Py_2 are synthesized and used for hydrogenation of 1'-acetonapthone. The activities and selectivities of the dipyridine precursors are compared to those of the corresponding DPEN-containing analogues, $RuCl_2$(diphosphine)(DPEN). The X-ray crystal structure of one of the dipyridine catalyst precursors, $RuCl_2$(JOSIPHOS)Py_2 is reported here for the first time. The dipyridine precursors were found to have good activities for the hydrogenation of 1'-acetonaphthone, but in comparison to the DPEN analogues their activities are lower.

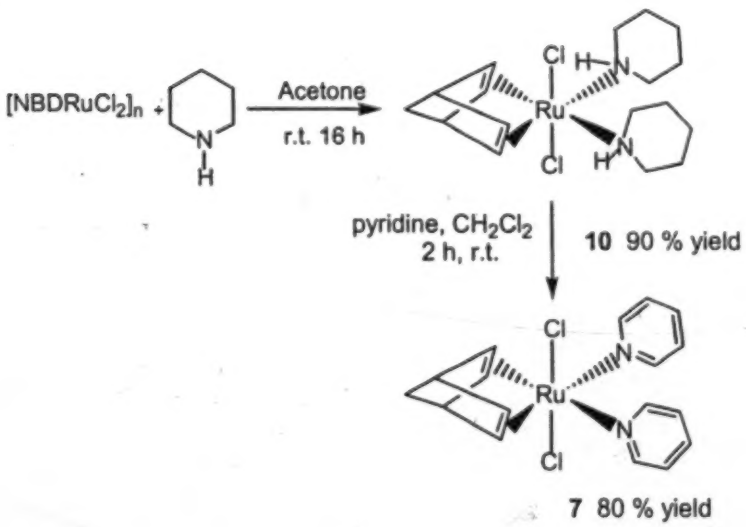
Results and Discussion

An improved synthesis of synthon for Ru(II)-diphosphine complexes. A versatile ruthenium chiral-diphosphine catalyst synthon, *trans*-$RuCl_2$(NBD)Py_2 **7,** was reported in chapter 2. Complex **7** reacts with a wide variety of structurally diverse diphosphine ligands to generate the catalyst precursors of the type *trans*-$RuCl_2$(diphosphine)Py_2 **8** by displacement of NBD. The catalyst precursors **8**[22] can be used to generate active catalysts for hydrogenation of different types of substrates including unfunctionalized ketones, β-ketoesters and α,β-unsaturated acids as described in Chapter 2. Compound **8** can also be easily converted to the Noyori type catalyst system, *trans*-$RuCl_2$(diphosphine)(DPEN), **9**, by reacting with either (*R*,*R*)- or (*S*,*S*)-DPEN at r.t. in CH_2Cl_2.

The utility of **7** as a general catalyst synthon was limited by a synthesis involving long reaction times and a tedious work-up procedure. The original preparation of **7** required stirring a mixture of $[RuCl_2(NBD)]_n$ in pyridine for eight days at r.t. Heating the mixture for shorter times resulted in formation of *trans*-$RuCl_2Py_4$ as a side product. In accord with the results of Potvin *et al.*[23] reaction of $[RuCl_2(NBD)]_n$ with five equivalents of piperidine at room temperature required only 16 h to form *trans*-$RuCl_2(NBD)(pip)_2$ (pip = piperidine) **10** in near quantitative yield without evidence of NBD displacement by piperidine. Unexpectedly it was found that, unlike in complex **7**, displacement of the NBD ligand in **10** was difficult. For example, there was no reaction between (*R*)-BINAP and **10** even after heating for 18 h in CH_2Cl_2.

Attempts were made to utilize *trans*-$RuCl_2(NBD)(DPEN)$ **11** as a catalyst synthon. Complex **11** was easily prepared by reaction of **7** and DPEN in CH_2Cl_2, but the NBD ligand in **11** was also difficult to displace by diphosphine ligands. The origins of the difference in rate of NBD displacement between **7**, **10** and **11** are unknown. The amine ligands in complexes **10** and **11** are more basic than Py and do not act as π-acids. As a result, the NBD ligand may be more strongly bonded to ruthenium in complexes **10** and **11** than in complex **7**. Alternatively, the reaction may occur by a prior dissociation of an amine ligand, and coordination of one end of the phosphine followed by NBD dissociation and pyridine probably dissociates more readily from ruthenium. Regardless, it was found that reaction of **10** with 180 equivalents of pyridine at r.t. for two hours displaces piperidine to form **7** in 80 % yield. Improved synthesis of **7** thus involves stirring $[RuCl_2(NBD)]_n$ in piperidine for 16 h at r.t. to form **10** in 90 % yield.

Scheme 3-5. Improved synthesis of catalyst synthon 7



This is then followed by reaction of **10** with excess pyridine for another 2 h at r.t. to give **7** in 80 % yield as shown in Scheme 3-5.

Complex **7** prepared according to Scheme 3-5 was used for the preparation of the following catalyst precursors by reaction with the appropriate diphosphines: $RuCl_2$ ((*R*)-BINAP)Py_2 (**8a**), $RuCl_2$((*S,S*)-CHIRAPHOS)Py_2 (**8b**), $RuCl_2$((*R,R*)-DUPHOS)Py_2 (**8c**) and $RuCl_2$((*R*)-(*S*)-JOSIPHOS)Py_2 (**8d**). The corresponding DPEN catalysts (**9a-9d**) were prepared by reaction of precursors of type **8** with (*R,R*)-DPEN. For example, the reaction of **8a** with (*R,R*)-DPEN formed the corresponding catalyst precursor $RuCl_2$((*R*)-BINAP)((*R,R*)-DPEN), **9a**. Compound **9b*** was obtained from **8b** by reaction with (*S,S*)-DPEN to give $RuCl_2$((*S,S*)-CHIRAPHOS)((*S,S*)-DPEN). The

complexes **8a**, **8b**, **9a** and **9c** were synthesized and characterized by both NMR and X-ray crystallography as described in Chapter 2. Attempts to obtain crystals of the compounds **8c**, **9b**, **9b*** and **9d** were unsuccessful. However, their NMR spectra indicated they probably have a *trans* disposition of chloride ligands similar to the other characterized compounds. None of the JOSIPHOS-containing precursors had been characterized by X-ray crystallography previously. A search through the Cambridge Crystal Structure Data Bank revealed that only two JOSIPHOS-ruthenium structures have been published before by Togni *et al.*[24] In order to elucidate the overall geometry of complex **8d** in the solid state, a single-crystal structure determination was done. Figure 3-1 shows the solid state structure of **8d**, and some selected bond lengths and bond angles pertaining to the structure are shown in Table 3-2. As expected from the structures in Chapter 2, the Ru centre in **8d** adopts a slightly distorted octahedral geometry with the Cl ligands in a mutually *trans* position and the Py ligands in mutual *cis* positions. The metal-ligand distances in this complex are comparable to those in Chapter 2 and also to those obtained in the compound [RuCl(*p*-cymene)((*R*)-(*S*)-JOSIPHOS)]$^+$.[24] The Ru-P bond distances corresponding to aryl (P1) and alkyl (P2) are slightly different, Ru-P1 being 2.2878(18)Å as compared to 2.3309(18)Å for Ru-P2. The shorter Ru-P1 bond could be caused by stronger back-donation from the metal to the less basic P1. Ru-Cl and Ru-N bond lengths are normal for JOSIPHOS-Ru complexes.[25] The bite angle, P-Ru-P, of the ligand in **8d** (88.5°) is somewhat smaller than that in the complex [RuCl(*p*-cymene)((*R*)-(*S*)-JOSIPHOS)]$^+$ (92.6°) perhaps due to unfavorable steric interactions between the bulky cyclohexyl rings and the Py ligands.

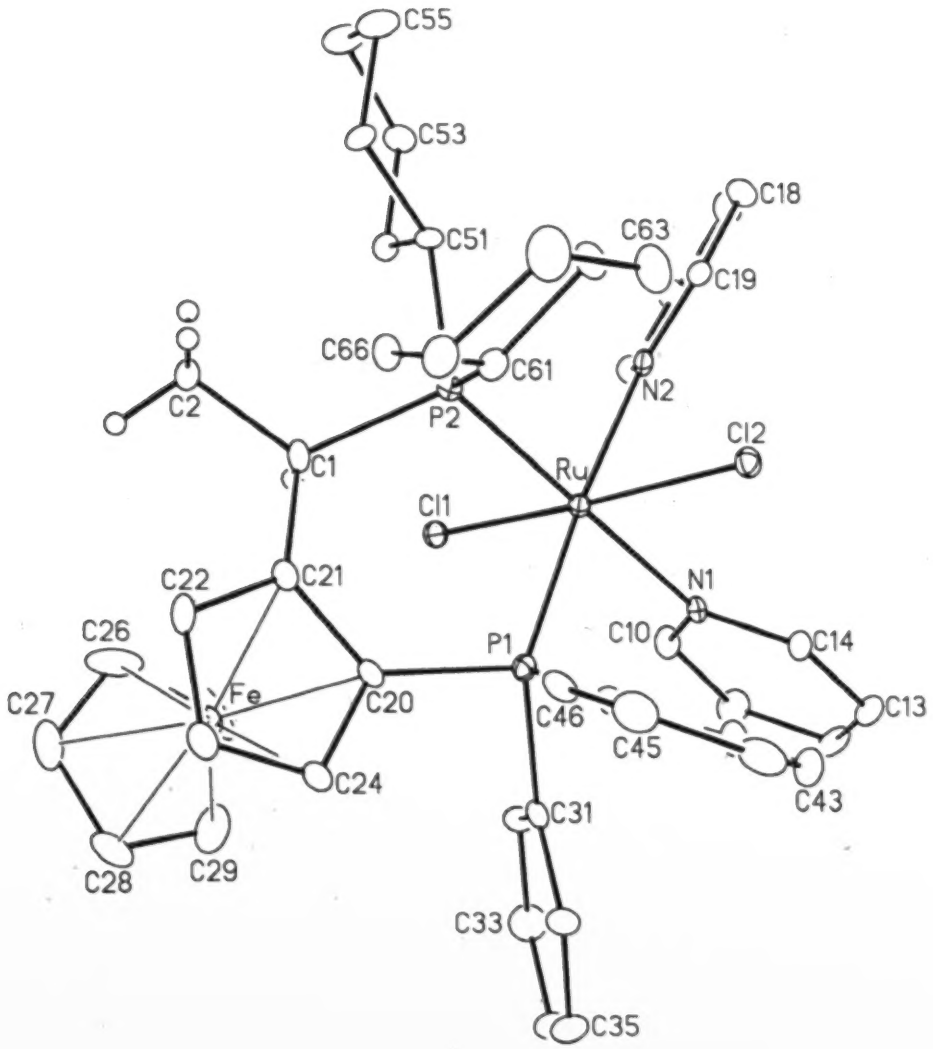
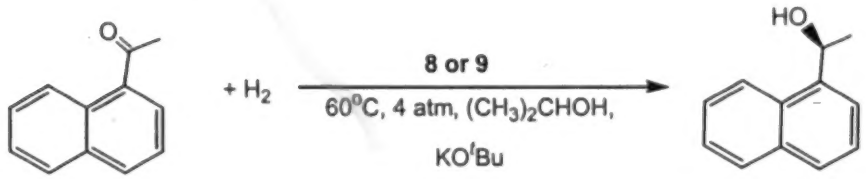


Figure 3-1. Perspective view of complex **8d** showing the atom numbering scheme. Hydrogen atoms on C(1) and C(2) are shown with arbitrarily small thermal parameters. All other hydrogen atoms have been omitted.

Table 3-2. Selected Interatomic Distances (Å) and Angles (deg) for 8d.

Ru–Cl1	2.4310(16)	P1–C41	1.844(7)
Ru–Cl2	2.4170(15)	P2–C1	1.870(5)
Ru–P1	2.2878(18)	P2–C51	1.852(6)
Ru–P2	2.3309(18)	P2–C61	1.865(6)
Ru–N1	2.233(5)	N1–C10	1.352(8)
Ru–N2	2.224(5)	N1–C14	1.340(7)
Fe–C20	2.072(6)	N2–C15	1.347(9)
Fe–C21	2.047(6)	C1–C2	1.548(8)
Fe–C22	2.058(7)	C1–C21	1.507(9)
Cl1–Ru–Cl2	173.51(6)	Cl2–Ru–N2	85.50(14)
Cl1–Ru–P1	93.35(6)	P1–Ru–P2	88.56(6)
Cl1–Ru–P2	90.43(6)	P1–Ru–N1	91.82(14)
Cl1–Ru–N1	89.13(13)	P1–Ru–N2	175.30(13)
Cl1–Ru–N2	88.47(14)	P2–Ru–N1	179.43(15)
Cl2–Ru–P1	92.48(6)	P2–Ru–N2	95.77(14)
Cl2–Ru–P2	92.56(5)	N1–Ru–N2	83.87(19)
Cl2–Ru–N1	87.85(13)	C20–Fe–C2l	40.9(2)

Catalysis reactions. The rates and selectivities of catalyst precursors **8a-d** for the hydrogenation of 1'-acetonaphthone (equation 3-3) were compared to those of the



(3-3)

DPEN containing analogues **9a-d**. The reactions are net hydrogenations as opposed to hydrogen transfer from 2-propanol since the conversion to product in absence of H_2 (g) is 5 % or less under similar conditions. The results obtained in this study are summarized in Table 3-3. From the data, the DPEN containing precursors are in general 2-3 times more active than their dipyridine counterparts (compare entries 1-4 to 5-9). Considering that the DPEN containing precursors are some of the fastest known catalysts for hydrogenation of alkyl-aryl ketones[9e] the activity obtained from dipyridine precursors is good and shows that the presence of primary or secondary amine is not mandatory for hydrogenation of simple ketones to proceed. This result is also supported by work reported by Fogg *et al.*[26] who found that the complex [*fac*-$RuH_3(CO)(dcypb)]^-$ was an active catalyst for reduction of benzophenone despite the absence of an amine group bearing an N-H bond. The use of the chiral diamine, (*R*,*R*)-DPEN, generally increased the ee values obtained with these catalyst systems. In most cases the increase was minor except for the BINAP ligand where the ee increased from 29 % to 82 %. For high ee values the absolute configuration of the diphosphine and the

Table 3-3. Hydrogenations of 1'-Acetonaphthone Catalyzed by Precursors 8 and 9[a]

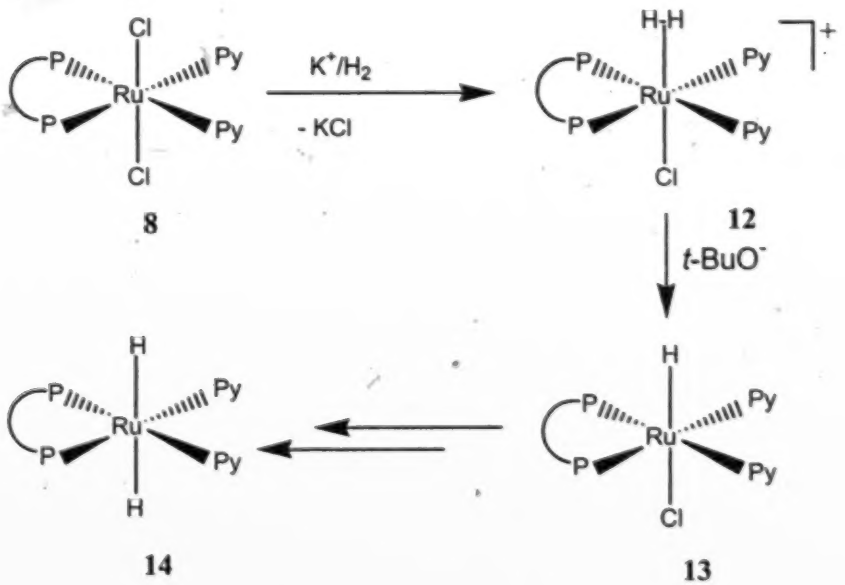
Entry	Cat	Phosphine	Amine	% Conversion	TOF (h^{-1})	% ee
1	**8a**	(*R*)-BINAP	Py	28	11.6	29 (*R*)
2	**8b**	(*S,S*)-CHIRAPHOS	Py	25	10.4	26 (*R*)
3	**8c**	(*R,R*)-Me-DUPHOS	Py	39	16.3	7 (*R*)
4	**8d**	(*R,S*)-JOSIPHOS	Py	26	10.8	14 (*S*)
5	**9a**	(*R*)-BINAP	(*R,R*)-DPEN	74	30.8	82 (*S*)
6	**9b**	(*S,S*)-CHIRAPHOS	(*R,R*)-DPEN	72	30.0	17 (*R*)
7	**9b***	(*S,S*)-CHIRAPHOS	(*S,S*)-DPEN	68	28.3	44 (*R*)
8	**9c**	(*R,R*)-Me-DUPHOS	(*R,R*)-DPEN	60	25.0	17 (*S*)
9	**9d**	(*R,S*)-JOSIPHOS	(*R,R*)-DPEN	83	34.6	55 (*S*)

[a]Hydrogenations done for 24 h in 2-propanol at 60^0C under 3.7 atm. dihydrogen, in presence of 1 mM catalyst, 4 mM KO^{t}Bu and 1.0 M substrate. Cat = catalyst

diamine should conform. For example if the absolute configuration of the phosphine is (*S,S*), high ees are obtained with the (*S,S*) enantiomer of DPEN (compare entry 6 and 7) as was observed previously by Noyori.[5] The reactivity obtained here using catalyst **9a** (TOF = 30.8 h^{-1}) is much lower than that obtained by Noyori using the same catalyst system (TOF = 82.5 h^{-1})[5] but the reasons for this difference were not investigated. Overall, for the phosphine ligands used, addition of DPEN resulted in only small improvements in ee values and thus the high ee values obtained in 'metal-ligand bifunctional catalysis' of the $RuCl_2$(diphosphine)(diamine) systems seem to be limited to BINAP and structurally related systems.

Probable hydrogenation mechanism for catalysts of type 8. The actual catalyst in complexes of type **8** is likely to be some hydride or dihydride species as is the case in hydrogen transfer catalysis[13,14] or in the Noyori-type complexes.[1,7,9,10] For these particular complexes, since they lack an NH bond, the Dcb mechanism (scheme 3-3) described earlier for the Noyori complexes is not possible for the generation of the hydride or dihydride species from the 18-electron dipyridine complexes. However, it is possible that such species could form by a process involving a prior dissociation of pyridine ligand(s) from alkoxides formed by reaction of complexes of type **8** with the

Scheme 3-6. Generation of dihydrides in dipyridine complexes

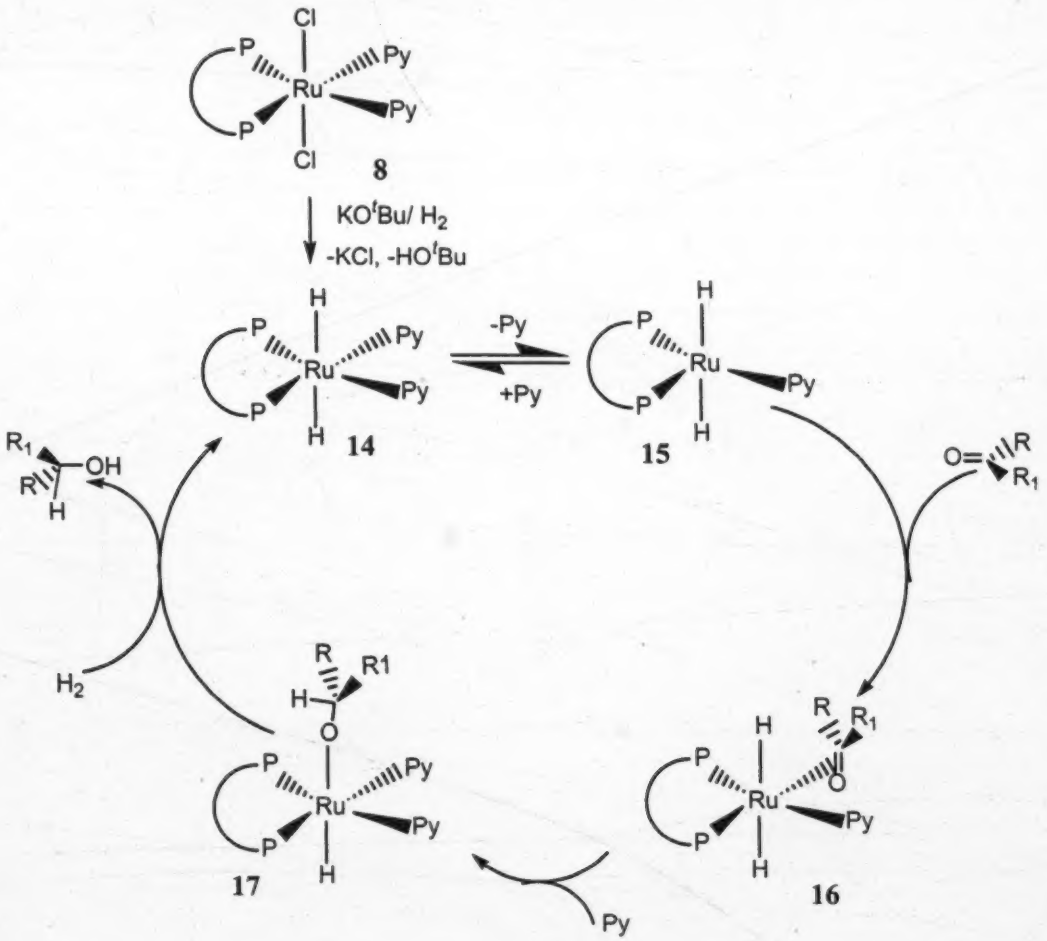


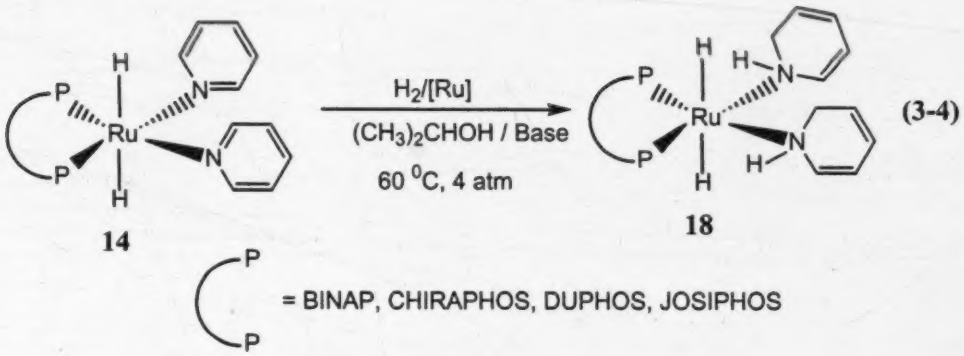
base. Alternatively, and perhaps more likely, the route to the dihydrides, starting from complexes of type **8** may involve a mechanism that forms η^2-dihydrogen intermediates, first reported by Morris *et al*[27] and shown in scheme 3-6. In this mechanism the halide

is eliminated as a salt from the dipyridine precursor to generate η^2-dihydrogen intermediate **12**. Proton abstraction from **12** by base gives **13**, the monohydride complex that could be the actual catalyst. In case the actual catalyst is a dihydride, the overall process if repeated, would generate **14**. The catalytic cycle is constructed based on a dihydride catalyst since more than one equiv. of the base was used to activate the dipyridine species. Once formed, the dihydride complex **14** can reversibly dissociate pyridine to generate the 16-electron complex **15** (scheme 3-7). Such dissociation of coordinated amine ligands has been proposed in Rh-catalyzed transfer hydrogenations of acetophenone and has been further substantiated by calculations.[28] Complex **15** can add a carbonyl to form the 18-electron species **16**. The ketone in **16** is likely η^2-bonded to the Ru center and inserts into the M-H bond via a concerted mechanism. Such a mechanism has been previously proposed in hydrogenation of aryl-alkyl ketones and aldehydes.[29] The ketone insertion, followed by recoordination of pyridine generates complex **17**. Hydrogenolysis of the metal-oxygen bond in **17** by dihydrogen gas would produce the alcohol and regenerate **14** to complete the catalytic cycle.

It is also conceivable that the hydrogenation of 1'-acetonaphthone could go by a pathway involving prior reduction of the pyridine ligands. Starting from the dihydride species **14**, hydrogenation of the pyridine would likely generate complex **18** (equation 3-4) that would then operate under the Morris/Noyori mechanism shown in scheme 3-4. This proposal is, however, highly improbable because, although homogeneous hydrogenation of pyridine is known, to the best of my knowledge, there are no known

Scheme 3-7. A probable mechanism of hydrogenation for dipyridine complexes





examples of homogeneous ruthenium based catalysts for this hydrogenation. The catalysts used are usually complexes of early first row transition metals such as vanadium[30] or titanium.[31] It is also known that under basic conditions, the ruthenium systems with primary or secondary amine ligands discriminate against hydrogenation of carbon-carbon multiple bonds. Indeed one of the major achievements of the metal-ligand bifunctional catalysis is the preferential hydrogenation of polarized bonds, for example, C=O or C=N over non-polarized bonds such as C=C as discussed previously (equation 3-1). It is therefore conceivable that the ruthenium catalyst system could hydrogenate species **14** to **18** in which only the C=N is reduced. But if this was the case, the rates of hydrogenation using complexes **8** should be comparable to those obtained using complexes **9** (Table 3-3) since the two systems would be expected to operate under similar mechanism. The lower rates of hydrogenation obtained by complexes of type **8** probably indicate a different mechanism is in operation using these catalyst precursors.

Conclusions

The discovery and development of $RuCl_2$(diphosphine))(diamine) catalysts precursors incorporating amine ligands with N-H bonds by Noyori *et al.*[1c,5] has revolutionized the field of enantioselective catalytic hydrogenation of ketones. The catalysts incorporating ligands with N-H groups are more active and are generally more selective than *trans*-$RuCl_2$(diphosphine)Py_2. The results presented in this chapter do show, however, that useful rates can be obtained in the absence of ligands with N-H groups. As such, they add flexibility to the design of catalyst precursors for such hydrogenation reactions. Consistent with this premise is the recent direct observation that addition of hydrogen and ruthenium across the ketone double bond is quite rapid in the absence of N-H groups for certain catalyst-ketone combinations.[32] Finally, the new synthesis of **7** facilitates its use as a general synthon for ruthenium-diphosphine catalysts.

Experimental

Materials and methods. All operations were performed under an inert atmosphere using standard Schlenk techniques. Dinitrogen gas (Praxair, 99.998%) was passed through a drying train containing 3Å molecular sieves and P_4O_{10} before use. Trace quantities of oxygen were removed from H_2 (Praxair, 99.99%) by passage through an Alltech Oxy-Trap. The solvents and reagents acetone (3Å sieves), dichloroethane (CaH_2), diethyl ether (K, Ph_2CO), *n*-hexane (K, Ph_2CO), methylene chloride (CaH_2), *iso*-propanol ($Mg(O^iPr)_2$), piperidine (CaH_2) and pyridine (CaH_2) were distilled from drying agents under nitrogen. The diphosphines ligand (*R*)-BINAP, (*S,S*)-CHIRAPHOS, (*R,R*)-DUPHOS and (*R*)-(*S*)-JOSIPHOS were used as received from Strem Chemical Co., Inc. Unless stated otherwise, all other reagents were obtained from Aldrich Chemical Co., Inc., of which the liquids were distilled before use. The glass pressure reactor was oven dried and silated before use using literature procedures.[33] $[RuCl_2(NBD)]_n$ was prepared according to published procedures[34] and catalyst precursors **8a**, **8b**, **8c**, **9a**, **9b** and **9c** were prepared as described in chapter 2.

Instrumentation. All ^1H, ^{13}C and ^{31}P NMR were measured on a Bruker AM-400 NMR spectrometer operating at 400.13 MHz, 100.16 MHz and 161.97 MHz respectively. ^1H and ^{13}C NMR chemical shifts are reported in parts per million (δ) relative to tetramethylsilane using the solvent as an internal reference. ^{31}P NMR chemical shifts are reported in parts per million (δ) relative to an 85 % H_3PO_4 external

reference. All ^{13}C and ^{31}P spectra are ^{1}H decoupled unless stated otherwise. Microanalysis were performed at the University of Alberta Microanalysis Laboratory. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm (sodium D line) using 1.0 dm cells. Gas chromatography (GC) was performed on a Supelco β-Dex 120 column (β-Dex) (30m x 0.25mm) fitted to a Hewlett-Packard 5980A gas chromatograph with a Hewlett Packard 3392A integrator.

Improved synthesis of catalyst synthon 7. *(a) Preparation of $RuCl_2(NBD)pip_2$ (10)*: The brown colored polymer $[RuCl_2(NBD)]_n$ (0.507 g, 1.92 mmol) was weighed in air and charged into a 50 mL r.b. flask with a side arm. The flask was deaerated by evacuating and refilling with dinitrogen gas. Dry, distilled and degassed acetone (2.3 mL) were added to the flask by syringe. This was followed by addition of 0.95 mL (0.817 g, 9.6 mmol.) of piperidine. The reaction mixture was then stirred at r.t. for 16 h under inert atmosphere. After completion of the reaction, 30 mL of hexanes was added to the flask with rapid stirring. The solution was allowed to stand for 15 min to allow the solid product to precipitate. The purple supernatant liquid was filtered and the residue washed twice with 10 mL of hexanes and pumped on high vacuo to give 0.78 g, (90 % yield) of yellow product, *trans*-$RuCl_2(NBD)Pip_2$. ^{1}H NMR (400.15 MHz, CD_2Cl_2): δ = 4.35 (apparent t, $^{3}J_{H\text{-}H}$ = 2.4 Hz, 4H, diene), 3.73 (m, 2H, *CH*, diene), 2.65 (m, 4H, $CH_{equatorial}$, amine), 2.40 (m, 6H, CH_{axial}, *NH* amine), 1.65 (m, 6H, $CH_{equatorial}$, amine), 1.44 (m, 2H, CH_2 diene) 1.35 (m, 6H, CH_{axial}, amine). ^{13}C [^{1}H] NMR (100.6 MHz, CD_2Cl_2): δ = 71.6 *C* = *C* (diene), 60.4 CH_2 (amine), 51.4 *CH* (diene), 48.7 CH_2 (amine) 28.5 CH_2 (amine) 24.1 CH_2 (diene). Elemental analysis: Found: % C, 46.57; H, 6.76; N, 6.31. Cald. C, 47.00; H, 6.96; N, 6.45.

(b) Preparation of $RuCl_2(NBD)Py_2$ 7 from 10. Into a 250 mL r.b. flask with side arm were charged 0.121 g (0.279 mmol) of **10**. This was followed by addition of 1 mL of CH_2Cl_2 . The yellow solution formed was stirred at r.t. for 10 min and then 4.1 mL, (3.97 g, 50 mmol) of pyridine were added to the reaction mixture. The solution was stirred for 2 h after which 100 mL of hexanes were added to precipitate the product. The product was recovered by filtration and washed twice with 10 mL of hexanes. The washings and filtrate were combined and concentrated on high vacuo. Hexanes (30 mL) were added to the concentrate for a second precipitation of product. Total recovered product was 0.094 g, 79.6 % yield of **7**.

Preparation of 8d and 9d. These compounds were prepared according to the general procedure described for compounds of the type $RuCl_2$(diphosphine)Py_2 and $RuCl_2$(diphosphine)(DPEN) described in Chapter 2.

***trans*-$RuCl_2$((*R*)-(*S*)-JOSIPHOS)Py_2 (8d).** ^{31}P NMR (162 MHz, CD_2Cl_2): δ 42.78 (d, J_{PP} = 42 Hz), 55.07 (d, J_{PP} = 42 Hz). ^1H NMR (400 MHz, CD_2Cl_2): δ 0.9-2.38 (br m, 25 H), 3.69 (s, 5H, cp), 4.07 (br s, 1H, cp), 4.15 (br s, 1H, cp), 4.60 (br s, 1H, cp), 4.93 (m, 1H, C*H*(Me)), 6.98 (t, J = 11.0 Hz, 2H), 7.0-7.7 (m, 12H, Ar), 8.04 (t, J = 10.8 Hz, 2H), 9.71 (br, 4H). Anal. Calcd for $C_{46}H_{54}Cl_2FeN_2P_2Ru$•0.5 CH_2Cl_2 : C, 59.75; H, 5.89; N, 3.03. Found: C, 59.65; H, 5.76; N, 2.67.

***trans*-$RuCl_2$((*R*)-(*S*)-JOSIPHOS)((*R,R*)-DPEN) (9d).** ^{31}P NMR (162 MHz, CD_2Cl_2): δ 48.91 (d, J_{PP} = 41 Hz, 1P), 56.74 (d, J_{PP} = 41 Hz, 1P). ^1H NMR (400 MHz, CD_2Cl_2): δ 0.9-2.38 (m, 25H), 3.69 (s, 5H, cp), 3.94 (br t, J = 12.0 Hz, 1H), 4.2-4.44 (m , 4H), 4.5 (m, 2H), 4.62 (s, 1H, cp), 4.67 (br s, 1H), 4.77 (br t, J = 15.6 Hz, 1H), 7.09-7.78 (br m, 16H), 8.39 (m, 1H), 8.65(m, 3H). Anal. Calcd for $C_{50}H_{60}Cl_2FeN_2P_2Ru$: C, 61.36; N, 2.86; H, 6.18. Found: C, 61.55; H, 6.12; N, 3.03.

Purification of commercial 1'-acetonaphthone. Freshly distilled 1'-acetonaphthone obtained from Aldrich Chemical Co. (10 mL) was placed in a 500 mL separatory funnel and 250 mL of dry ethyl ether were added. The flask was shaken to ensure a homogeneous mixture. The mixture was washed by 0.1 M KOH solution (3 x 30 mL). The aqueous layer was discarded whereas the organic layer was collected and transferred into a 300 mL Erlenmeyer flask and dried over anhydrous Na_2SO_4 for 2 h. The solvent was pumped off on a rotovap to leave behind 1'-acetonapthone as a clear colorless viscous liquid that was distilled under reduced pressure.

General procedure for hydrogenation carried out with 8 or 9 as catalyst precursors. The catalyst precursor (0.0108 mmol) and the base (KO^tBu, 0.0432 mmol) were weighed in the glove box and charged into a glass pressure reactor containing a magnetic stirbar. Dry, distilled *iso*-propanol (10.8 mL) was added to the reactor using a syringe. The catalyst precursor dissolves forming a yellow-amber solution on stirring for a few minutes. The argon-saturated (bubbled 20 min) substrate (1.84 g 10.8 mmol) is then introduced using a syringe. Dihydrogen gas was bubbled through the solution with rapid stirring for 10 min. The septum was replaced with the pressure lid of the reactor, and the system pressurized (40 psi gauge pressure) and vented three times with dihydrogen gas before being pressurized to 40 psi (gauge pressure) and placed in a 60 ^{0}C oil bath with rapid stirring for 24 h. The solutions tend to turn red-amber during the hydrogenations. The mixture was then cooled, depressurized and flushed with dinitrogen. The product was recovered by pumping off the solvent on a rotovap.

Product work-up and determination of the absolute configuration. The catalyst residues were removed from the products by dissolving the product in ethyl acetate and passing the mixture through a florisil plug. The solvent was then removed on the rotovap. Percentage conversion to product and the enantiomeric excess was obtained by chiral GC analysis (150°C, 8 psi head pressure, retention time reactant 38.4 min; (*S*)-enantiomer 62.6 min; (*R*) enantiomer 64.4 min). The absolute configuration was assigned by comparing the optical rotation to that reported in the literature.[36]

X-ray crystallography. Crystals of **8d**•$0.5C_2H_4Cl_2$ suitable for structure determination by X-ray diffraction were obtained by slow liquid-liquid diffusion of hexanes into a saturated solution of **8d** in 1,2-dichloroethane at -10 ^{0}C. Data collection, structure solution and structure refinement for **8d** were performed by Dr. Michael Ferguson, Faculty Service Officer, Structure Determination Laboratory, Department of Chemistry, University of Alberta. See table 3-2 for some selected bond lengths and bond angles for **8d**. Table 3-4 gives a summary of crystal data collection, structure solution and structure refinement information for **8d**•$0.5C_2H_4Cl_2$. Final atomic coordinated and displacement parameters may be obtained from X-ray Crystallography Laboratory, Department of Chemistry, University of Alberta with a file code SHB0208.

Table 3-4. Crystallographic Experimental Details for 8d•0.5$C_2H_4Cl_2$

A. Crystal Data	
formula	$C_{47}H_{56}Cl_3FeN_2P_2Ru$
formula weight	974.15
crystal dimensions (mm)	0.15 x 0.12 x 0.10
crystal system	orthorhombic
space group	$P2_12_12$ (No. 18)
unit cell parameters[a]	
a (Å)	22.663 (3)
b (Å)	13.3050 (15)
c (Å)	14.5132 (16)
V (Å^3)	4376.2 (8)
Z	4
ρcalcd (g cm^{-3})	1.479
μ (mm^{-1})	0.969
B. Data Collection and Refinement Conditions	
diffractometer	Bruker PLATFORM/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ω scans (0.2°) (25 s exposures)
data collection 2θ limit (deg)	52.90
total data collected	24602 ($-28 \le h \le 25$, $-16 \le k \le 16$, $-18 \le l \le 15$)
independent reflections	9008 (R_{int} = 0.0985)
number of observed reflections (*NO*)	6545 [$F_o^2 \ge 2\sigma(F_o^2)$]
structure solution method	direct methods (*SIR97*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–93*[d])
absorption correction method	empirical (*SADABS*)
range of transmission factors	0.9093–0.8683
data/restraints/parameters	9008 [$F_o^2 \ge -3\sigma(F_o^2)$] / 0 / 505
Flack absolute structure parameter[e]	–0.02(3)
goodness-of-fit (*S*)[f]	1.027 [$F_o^2 \ge -3\sigma(F_o^2)$]
final R indices[g]	
R_1 [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0565
wR_2 [$F_o^2 \ge -3\sigma(F_o^2)$]	0.1107
largest difference peak and hole	0.685 and –0.549 e Å^{-3}

[a]Obtained from least-squares refinement of 3739 reflections with $4.53° < 2\theta < 47.17°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **1999**, *32*, 115–119.

[d]Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993. Refinement on F_O^2 for all reflections (all of these having $F_O^2 \geq -3\sigma(F_O^2)$). Weighted R-factors wR_2 and all goodnesses of fit S are based on F_D^2; conventional R-factors R_1 are based on F_O, with F_O set to zero for negative F_O^2. The observed criterion of $F_O^2 > 2\sigma(F_O^2)$ is used only for calculating R_1, and is not relevant to the choice of reflections for refinement. R-factors based on F_O^2 are statistically about twice as large as those based on F_O, and R-factors based on ALL data will be even larger.

[e]Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr.* **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst.* **2000**, *33*, 1143–1148. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration.

[f]$S = [\Sigma w(F_O^2 - F_C^2)^2/(n-p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_O^2) + (0.0400P)^2]^{-1}$ where $P = [\text{Max}(F_O^2, 0) + 2F_C^2]/3$).

[g]$R_1 = \Sigma||F_O| - |F_C||/\Sigma|F_O|$; $wR_2 = [\Sigma w(F_O^2 - F_C^2)^2/\Sigma w(F_O^4)]^{1/2}$.

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CHAPTER 4†

Synthesis of a PennPhos Ruthenium(II) Complex: The First Crystal Structure of a PennPhos-Metal Complex

Introduction

Complexes of ruthenium(II) and chiral diphosphines are the most successful catalyst systems for the enantioselective hydrogenation of prochiral olefins and ketones.[1,2] Recently a versatile procedure to synthesize ruthenium-diphosphine catalyst precursors that complements the existing procedures in the literature was reported.[3] It was shown that most common chiral diphosphine ligands react with the complex *trans*-$RuCl_2(NBD)Py_2$ (**1**) to generate in high yields the crystalline complexes *trans*-$RuCl_2(P\text{-}P^*)Py_2$ (P-P* is the corresponding chiral diphosphine). Examples of *trans*-$RuCl_2(P\text{-}P)Py_2$ and similar compounds have been reported previously by the James' group.[4] These complexes were found to be active enantioselective hydrogenation catalysts for keto esters and for non-carboxylic olefins in the presence of small amounts of HBF_4(aq.).[3] Further, reaction of these complexes with 1,2-diphenylethylenediamine (N-N*, either enantiomer) formed in good yields[3] the corresponding compounds developed by the

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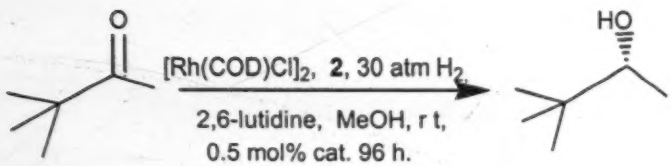
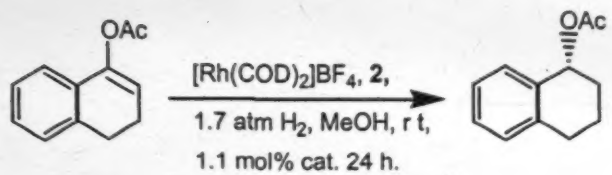
Noyori group, *trans*- $RuCl_2(P\text{-}P^*)(N\text{-}N^*)$, that are well-known, extremely active chemo- and enantioselective hydrogenation catalysts for simple aryl-alkyl ketones.[1,2]

Recently Zhang *et al.*[5] reported the synthesis of a conformationally rigid diphosphine ligand, Me-PennPhos (**2**) (see figure 4-2). A rhodium complex of **2** currently gives the highest enantioselectivity reported to date for hydrogenation of simple

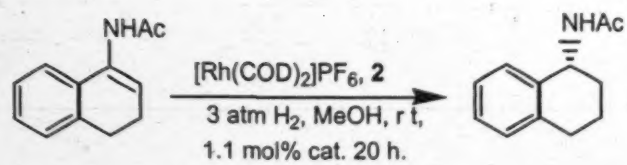


94 % ee **(4-1)**

dialkyl ketones (equation 4-1).[5,6] In addition, rhodium complexes of ligand **2** are also highly selective for hydrogenation of cyclic enol acetates[7] (equation 4-2) and cyclic enamides[8] (equation 4-3). The high selectivities of these catalyst systems have been



99.1 % ee **(4-2)**



98 % ee **(4-3)**

attributed to the design features of **2**, namely C_2-disymmetry, large projection into the spatial domain of the coordinated prochiral substrate, and conformational rigidity.

C_2-Symmetry is a popular design element for chiral diphosphine ligands as it reduces the number of possible competing diastereomeric transition states.[9] In a square planar complex, for example, coordination of a C_2-symmetric bidentate ligand leaves two vacant coordination sites. These sites are interrelated by the C_2-axis of symmetry and are therefore equivalent (figure 4-1). In octahedral complexes, the presence of a C_2- axis

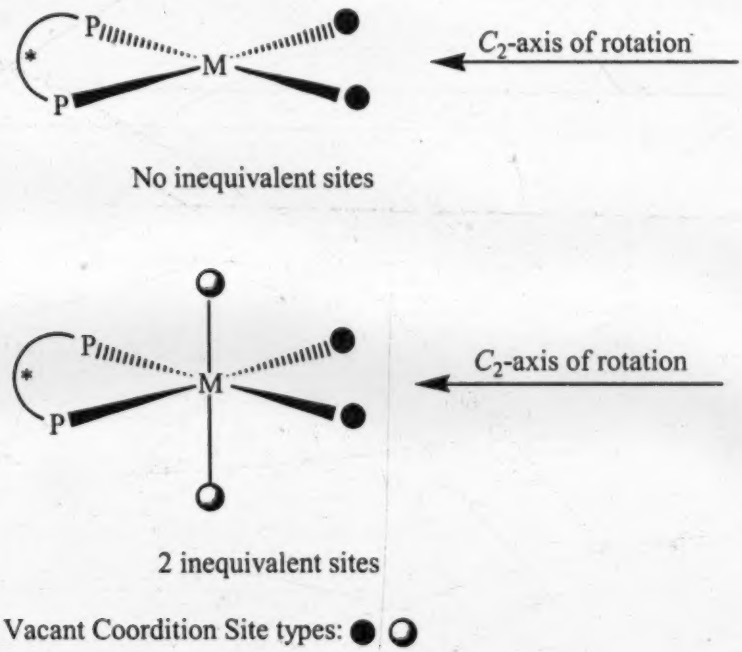
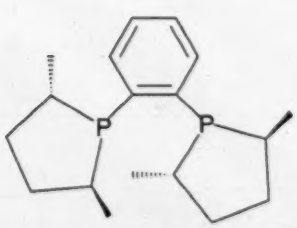


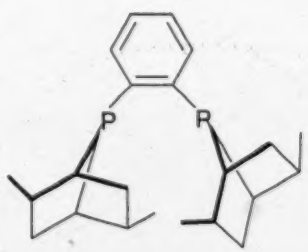
Figure 4-1. Coordination sites of C_2-symmetric metal species.

reduces the number of vacant inequivalent sites to two (figure 4-1). In both cases, the number of possible diastereomers is less than that of a complex containing either chiral monodentate or non-symmetric polydentate ligands. With the number of diastereomeric intermediates reduced, the number of possible reaction pathways is also reduced and the likelihood of high enantioselection is increased.

Conformational rigidity is also an important component of successful diphosphines for enantioselective hydrogenation. Its importance can be understood from the standpoint of steric interactions between the diphosphine and the coordinated substrate. If the diphosphine is conformationally flexible, unfavourable steric interactions with the substrate could cause it to adjust the orientation of its ancillary groups away from the coordinated substrate. Another component of flexibility is that the net asymmetric induction is the weighted average of each conformation a diphosphine adopts in a diastereomeric catalyst-substrate complex.[9b] Therefore the more conformations available, the lower the net asymmetric induction.



(*S*,*S*)-Me-DUPHOS



2

Figure 4-2. Structures of (*S*,*S*)-Me-DUPHOS and Me-PennPhos **2**.

Ligand **2** is C_2-symmetric and shares some features with Me-DUPHOS such as electron-donating properties and modular structure; both ligands have the 1,2-bis(phospholano)benzene structural motif (figure 4-2). However, unlike DUPHOS, **2** was designed with a fused rigid bicyclic [2.2.1] heptane structure which eliminates the conformational flexibility associated with five membered rings.[10] As has been discussed, such conformational changes result in reduced selectivity. In addition, the projection of Me groups into the spatial domain of the coordinated substrate is expected to further enhance the stereoselectivity of **2**. Quite unexpectedly, reaction of **2** with Rh metal precursors does not result in C_2-symmetric compounds.[5] The reasons for this anomaly have not been clarified because, until this work was reported, there were no well-characterized metal complexes of **2**. All hydrogenations reported using rhodium complexes of **2** have been done with *in situ* addition of the ligand to the metal precursor complexes (equations 4-1- 4-3).[5,7,8]

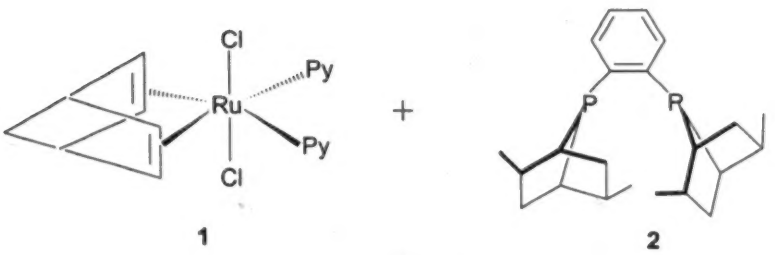
It was generally assumed that the ligand structure in these complexes was C_2-disymmetric and the high enantioselectivities obtained could be accounted for by this structural feature. This chapter describes work carried out to obtain the first crystal structure of a metal-PennPhos compound. It was found that ligand **2** reacts with the ruthenium precursor **1** not to form the monomeric dichlorides obtained with most common chiral diphosphine ligands, but rather to form cationic triply chloro-bridged dimers in which the ligand adopts a bent, non C_2-symmetric geometry upon coordination to ruthenium.

Results and Discussion

Synthesis and characterization of a PennPhos-ruthenium complex. (*R*,*S*,*R*,*S*)-Me-PennPhos **2** reacts cleanly with **1** to generate two diastereomers of the triply chloride-bridged cationic dimer **3**, as illustrated in Scheme 4-1. Related monocationic dimers containing nitrile ligands and mono- or bidentate phosphine ligands have been reported by the James group.[4b,11] At room temperature, this reaction proceeds to give two diastereomers of **3** in the ratio ~ 2:3. The ratio of diastereomers formed is dependent on the reaction temperature. If the reaction is carried out at 45 ^{0}C, the minor diastereomer formed at room temperature is then formed as the major diastereomer in a ratio ~ 3:1. The major diastereomer formed at 45 ^{0}C was identified as one of the *anti*- diastereomers by X-ray diffraction *vide infra*. If made at room temperature, the ratio of diastereomers (~ 2:3) converts to the limiting ratio (~ 3:1) upon heating the reaction mixture at 45 ^{0}C overnight. These observations suggest that the major diastereomer formed at room temperature is a kinetic product that is thermodynamically less stable than the other diastereomer. Further, it appears that the diastereomers interconvert slowly at 45 ^{0}C. Similar interconversions have been observed, for example, with ruthenium diphosphine complexes such as $RuCl_2(dppb)(L)_2$ { L = NH_3, Py, 4-NH_2Py, 4-CNPy, 4-MePy, 4-PhPy}.[4b,4c,12]

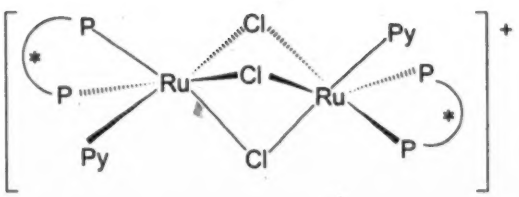
Diastereomers of the complex. There are three possible diastereomers of **3**, two with *anti* relative orientations of the Py rings, and one with a *syn* orientation. Scheme 4-1 shows the *syn*- diastereomer and the two *anti*- diastereomers. A similar situation was

Scheme 4-1. Reaction of 1 and 2



1 + 2

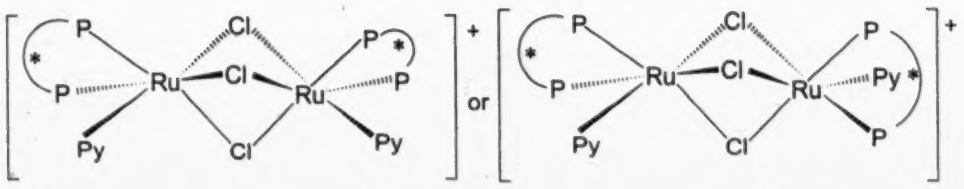
CD_2Cl_2 | 45°C



+ minor isomer

3 (*anti*) 3 : 1

minor isomer is



syn *anti*

observed by James *et al.*[4b,12] for other Ru(II) triply chloro-bridged dimers. The $^{31}P\{^{1}H\}$ spectrum of the minor diastereomer of **3** formed at 45 °C exhibits an AB pattern with two doublets at $\delta = 62.7$ and $\delta = 87.9$. The major *anti*- diastereomer shows a similar pattern, but with peaks at $\delta = 68.7$ and $\delta = 82.8$. As the two possible minor diastereomers of **3** have two-fold rotation axes, NMR spectroscopy could not be used to distinguish between them.

The dimeric structure of **3**, and the identity of the major diastereomer formed at 45 °C, were confirmed by X-ray crystal studies. Yellow crystals of major *anti*-**3** were obtained upon crystallization by layering hexanes onto a dichloromethane solution of **3**. Dissolution at low temperature in CD_2Cl_2 and NMR spectroscopy confirmed that these crystals are of the major diastereomer formed at 45 °C. The compound crystallizes with three molecules of CD_2Cl_2 per molecule of complex. The structure formed is a distorted octahedral configuration around the Ru center with the Cl ligands in a *facial* arrangement. The two P and the Py ligand occupy remaining positions on the octahedral as shown in Figure 4-3. There are four molecules of **3** per unit cell arranged as shown in Figure 4-4.

Face-sharing bioctahedral structure. The structure of **3** is a triply-bridged diruthenium(II, II) face-sharing bioctahedron. Similar X-ray structures for Ru(II, II) dinuclear species have been reported with diphosphine [4d,12] or monophosphine[13] ligands coordinated to the metal center. The Ru-Ru internuclear distance obtained for this compound is 3.289 Å, a distance much longer than a typical Ru-Ru single bond (2.632-3.034 Å)[14] indicating that there is no bonding between the Ru atoms. The Ru-Ru

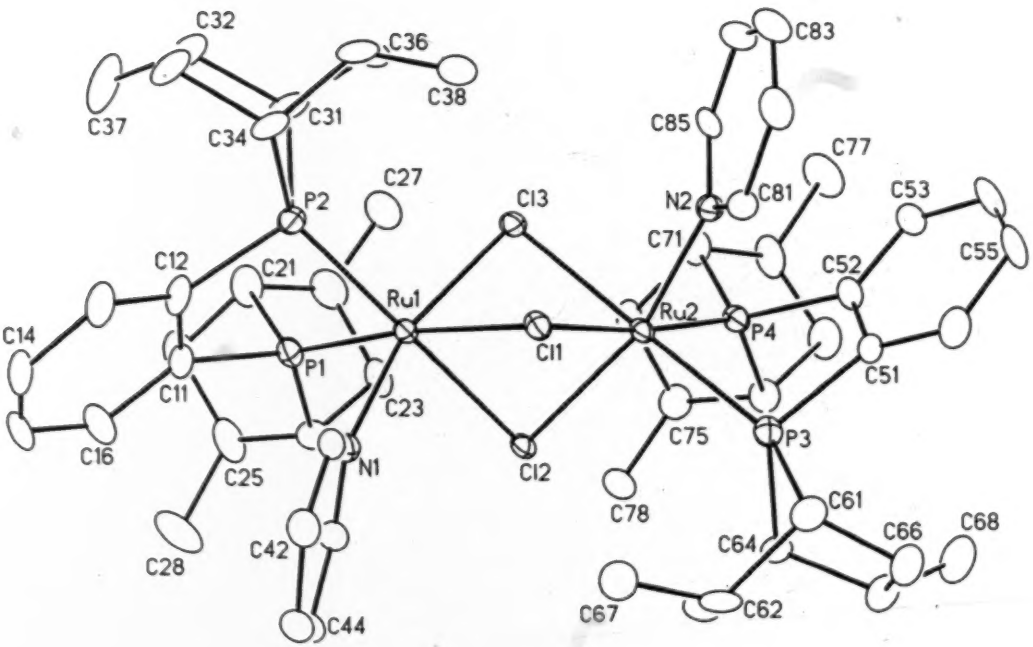


Figure 4-3. Perspective view (ORTEP) of the major diastereomer of the cation *anti*-**3** (20% thermal ellipsoids) showing the atom numbering scheme. Hydrogen atoms have been omitted for clarity. The Cl^- counter ion is also not shown.

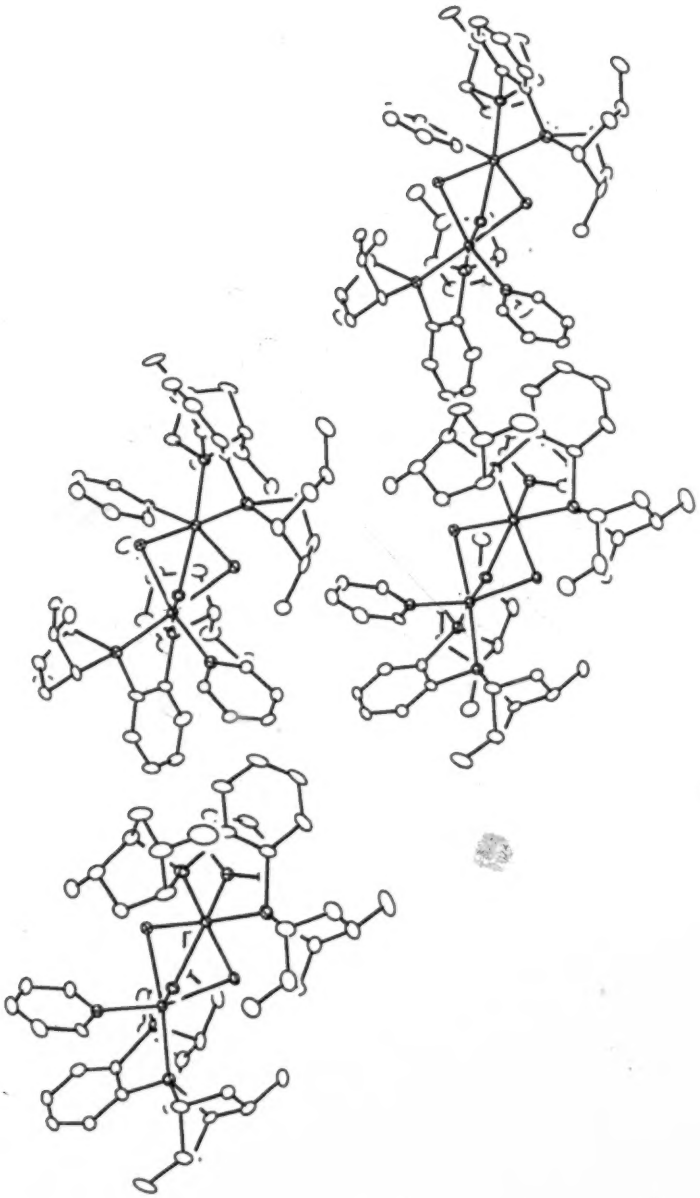


Figure 4-4. Spatial distribution within the unit cell of the major *anti*- diastereomer of **3**.

distance in this compound is, however, within the range expected for diruthenium complexes with triply-bridging Cl atoms. Some examples and their respective Ru-Ru distances are as follows: $[H_2NEt_2][Ru_2Cl_5((R)$-*p*-MeO-BINAP$)_2]$, 3.3 Å;[15] $[Ru_2Cl_4(dppb)_2$ η^2-$H_2]$, 3.278 Å;[4d] and $[Ru_2Cl_3(PBu_3)_6][BPh_4]$, 3.39 Å.[13] The Ru-Cl and Ru-N distances fall within the expected ranges for such Ru(II) complexes.[4a,4c,4e,16,17] Table 4-1 lists some selected interatomic distances within the major *anti*-**3** diastereomer.

Table 4-1 also lists some selected interatomic angles for major *anti*-**3**. Of interest is the marked contraction of the Cl-Ru-Cl angle (average 80.9 °) from the expected 90° for a regular octahedral. This contraction has been explained by Cotton and Torralba[13] to result from repulsive forces between the two d^6 Ru(II) centers in the molecule with consequent increase in Ru-Ru internuclear distance. The increased Ru-Ru internuclear distances result in contraction of the Cl-Ru-Cl bond angles and expansion of the Ru-Cl-Ru angles. The average values for the angles obtained in this compound for Cl-Ru-Cl and Ru-Cl-Ru (83.6°) fall within the expected respective ranges (77.2-80.9°) and (82.9-87.9°) for this type of complexes.[4d,12,13,14]

The bis(phospholano)benzene ligands such as Me-DUPHOS are known to form Ru complexes in which the P atoms, Ru atom and the aryl ring are all in the same plane.[3,18] Compound **3** is expected to have a similar structure to the Me-DUPHOS-Ru complexes. Unexpectedly in compound **3** the PennPhos P-aryl-P plane is tilted relative to the P-Ru-P plane. This tilt removes the C_2-dissymmetry of the ligand. While it is not known whether this tilting is typical of PennPhos compounds, we note that Zhang *et al.*[5] observed that the $^{31}P\{^1H\}$ NMR spectrum of [Rh(**2**)(COD)]$^+$ contained two sets of

Table 4-1. Selected Interatomic Distances (Å) and Angles (deg) for *anti*-3•3CD_2Cl_2

Ru1–Cl1	2.456(19)	Ru2–P3	2.26(2)
Ru1–Cl2	2.515(18)	Ru2–P4	2.286(18)
Ru1–Cl3	2.439(18)	Ru2–N2	2.09(6)
Ru1–P1	2.28(2)	P1–C11	1.85(8)
Ru1–P2	2.26(2)	P2–C12	1.83(9)
Ru1–N1	2.09(6)	P3–C51	1.85(8)
Ru2–Cl1	2.4662(18)	P4–C52	1.82(8)
Ru2–Cl2	2.435(17)	N1–C41	1.32(10)
Ru2–Cl3	2.50(2)	N2–C85	1.37(10)
Cl1–Ru1–Cl2	79.9(6)	Cl1–Ru2–Cl2	81.4(6)
Cl1–Ru1–Cl3	81.9(6)	Cl1–Ru1–Cl3	80.7(6)
Cl1–Ru1–P1	173.4(8)	Cl1–Ru2–P3	102.9(7)
Cl1–Ru1–P2	102.9(7)	Cl1–Ru2–P4	173.3(7)
Cl1–Ru1–N1	84.4(17)	Ru1–P1–C11	100(3)
Cl2–Ru1–Cl3	79.0(6)	Ru1–P2–C12	101(3)
Cl2–Ru1–P1	97.8(7)	P1–Ru1–P2	79.5(8)
Cl2–Ru1–P2	176.7(7)	P1–Ru1–N1	89.4(17)
Cl2–Ru1–N1	89.3(17)	P3–Ru2–P4	78.3(7)
Cl3–Ru1–P1	103.8(7)	P3–Ru2–N2	92.8(17)
Cl3–Ru1–P2	99.6(7)	Ru1–Cl1–Ru2	83.9(6)
Cl3–Ru1–N1	163.4(17)	Ru1–Cl2–Ru2	83.3(5)

signals for the phosphorus centers, showing they were inequivalent. A possible explanation put forward by Zhang *et al.* was that the phosphabicyclo[2.2.1]heptane groups are too bulky to allow the PennPhos to adopt a planar, C_2-symmetric geometry. The results obtained in the present work appear to confirm this explanation.

Conclusions

The work presented in this chapter further illustrates the versatility of compound **1** as a starting material for preparation of various Ru(II)-diphosphine complexes. The reported crystal structure is the first of a metal complex containing the PennPhos ligand. The formation of dimers upon reaction of **1** with PennPhos rather than the monomeric species formed with most common chiral diphosphine ligands[3] illustrates how the structure of the diphosphine ligand can have unexpected consequences on the structures of their metal complexes. Specifically, two methyl groups of PennPhos (in this case, C38 and C27 as well as C67 and C78 of major *anti*-**3**) project into the spatial domain occupied by other ligands on the catalyst centre. It is proposed that this projection favors formation of cationic dimers **3**, rather than the corresponding monomeric dipyridine complex *trans*-$RuCl_2$(Me-PennPhos)Py_2. Inspection of molecular models of *trans*-$RuCl_2$(Me-PennPhos)Py_2 and the solid-state structure of major *anti*-**3** shows that the methyl groups (e.g. C67, C38) in *trans*-$RuCl_2$(Me-PennPhos)Py_2 would protrude into the spatial domain occupied by the Py ligands.[3,4c] No such steric congestion is present in major *anti*-**3** because of its dimeric structure. Further, since we have shown previously[3] that

reaction of (*R*,*R*)-Me-DUPHOS with **1** generates the monomeric complex *trans*-$RuCl_2$((*R*,*R*)-Me-DUPHOS)Py_2, the present results indicate that it is more the steric requirements, and less the electronic requirements of Me-PennPhos, that govern formation of the cationic dimers **3**.

Experimental Section

Instrumentation. All ^1H and ^{31}P NMR spectra were measured on a Bruker AM-400 spectrometer operating at 400.13 MHz and 161.97 MHz, respectively, or on a Bruker AM-200 spectrometer operating at 200.13 MHz and 80.02 MHz, respectively. ^1H NMR chemical shifts are reported in parts per million (δ) relative to tetramethylsilane using solvent as an internal reference. ^{31}P NMR chemical shifts are reported in parts per million (δ) relative to an 85% H_3PO_4 external reference.

Reagents and Solvents. The solvents and reagents, n-hexanes (K, Ph_2CO), methylene chloride-d_2 (CaH_2), and pyridine (CaH_2) were distilled from drying agents under argon. The argon gas was passed through a bed of Drierite drying agent. Compound **1** was prepared as described in Chapter 2.

General Methods. Unless stated otherwise, all manipulations were carried out in oven dried glassware using standard air-sensitive techniques.

[{Ru(Me-PennPhos)Py}$_2$(μ-Cl)$_3$][Cl$^-$] (3). Compound **2** (17.0 mg, 0.0474 mmol) and 20.03 mg (0.0474 mmol) of **1** were weighed in air and charged into an NMR tube. The tube was sealed with a rubber septum and the contents flushed with argon gas. Dry

degassed methylene chloride-d_2 (0.5 mL) was added to the tube by cannula and the tube shaken to dissolve the solids. The septum was further wrapped with paraffin film to attach it firmly onto the tube. NMR spectroscopy showed that the reaction was ~ 70 % complete after 20 h at room temperature. The reaction was complete in less than 16 h when carried out at 45 ° C. The original orange /brown solution of the starting materials gradually turns yellow during this period.

Separation of Diastereomers. An NMR tube containing the CD_2Cl_2 reaction mixture was cooled to -78 ^{0}C (with dry-ice/acetone) and layered with hexanes that were added slowly and drop-wise to ensure that the drops flowed down the walls of the tube were cooled before coming into contact with the reaction mixture. The tube was then carefully removed from the cold bath and stored for 5 days at 8 ^{0}C. The major diastereomer of *anti*-**3** formed as yellow crystals suitable for X-ray analysis. The other isomer of **3** remained in solution. The crystals were recovered by filtration using a cannula with filter paper. NMR spectroscopy showed that the crystals contained only the major *anti*-diastereomer of **3**.

NMR Data for 3. Isolated major *anti*-isomer: ^{31}P NMR{^{1}H}(162 MHz, CD_2Cl_2); δ = 82.8 (d, $^2J_{pp}$ = 32 Hz); 68.7 (d, $^2J_{pp}$ = 32 Hz). ^{1}H NMR (400 MHz, CD_2Cl_2); δ = 8.25 (m, 4H, Ar); 7.26 (m, 6H, Ar); 6.63 (m, 8H, Ar); 2.98 (d, 2H, $^2J_{PH}$ = 10 Hz, PC*H*); 2.85-2.75 (br m, 4H, PC*H*); 2.52 (d, 2H, $^2J_{PH}$ = 10 Hz, PC*H*); 2.43-1.66 (br m, 12H); 1.51 (d, 6H, $^3J_{HH}$ = 9 Hz, CH_3); 1.46 (d, 6H, $^3J_{HH}$ = 9 Hz, CH_3); 0.76 (d, 6H, $^3J_{HH}$ = 7 Hz, CH_3); 0.62 (d, 6H, $^3J_{HH}$ = 7 Hz, CH_3).

Minor isomer:[19] ^{31}P NMR {^{1}H}(162 MHz, CD_2Cl_2); δ = 87.9 (d, $^2J_{pp}$ = 32 Hz); 62.7 (d, $^2J_{pp}$ = 32 Hz). ^{1}H NMR (400 MHz, CD_2Cl_2); δ = 8.46 (m, 4H, Ar); 7.71-7.35 (br

m, 6H, Ar); 7.05 (m, 8H, Ar); 2.75-2.68 (m, 4H, PC*H*); 2.43 (d, 2H, $^2J_{PH}$ = 18 Hz, PC*H*); 2.33-2.15 (br m, 12H); 1.15 (d, 6H, $^3J_{HH}$ = 7 Hz, CH_3); 1.02 (d, 6H, $^3J_{HH}$ = 7 Hz, CH_3); 0.67 (d, 6H, $^3J_{HH}$ = 7 Hz, CH_3); 0.57 (d, 6H, $^3J_{HH}$ = 7 Hz, CH_3).

X-ray Crystallographic Studies. Yellow crystals of the major diastereomer of *anti*-**3** · 3CD_2Cl_2 were obtained from slow diffusion of hexanes into CD_2Cl_2 as has been described above. Data were collected on a Bruker P4/RA/SMART 1000 CCD[20] diffractometer using Mo Kα radiation at -80 °C. Unit cell parameters were obtained from a least squares refinement of the setting angles of 5574 reflections from the data collection. The monoclinic diffraction symmetry and systematic absences indicated the space group to be *C*2 (No. 5). The data were corrected for absorption through use of *SADABS*[21] procedure. See Table 4-2 for a summary of crystal data and X-ray data collection information. The structure of the compound was solved using the *DIRDIF-96* program system,[22] and refinement was completed using the program *SHELXL-93*.[23] Hydrogen atoms were assigned positions based on the geometries of their attached carbon atoms, and were given thermal parameters 20 % greater than those of the attached carbons. Distance restraints were employed to impose an idealized geometry upon one of the solvent dichloromethane molecules: d(Cl(6S)-C(4S)) = d(Cl(6S)-C(4S)) = 1.80 Å; d(Cl(6S)…Cl(7S)) = 2.95 Å. The final model for the compound refined to values of $R_1(F)$ = 0.0639 (for 8806 data with $F_o \geq 2\sigma(F_o^2)$) and $wR_2(F^2)$ = 0.1993 (for all 12330 independent data). Final atomic coordinated and displacement parameters may be obtained from X-ray Crystallography Laboratory, Department of Chemistry, University of Alberta with the file code SHB 9907.

Table 4-2. Crystallographic Experimental Details for *anti*-3•3CD_2Cl_2

A. Crystal Data

formula	$C_{57}H_{80}Cl_{10}N_2P_4Ru_2$
formula weight	1473.75
crystal dimensions (mm)	0.34 × 0.17 × 0.07
crystal system	monoclinic
space group	*C2* (No.5)
unit cell parameters[a]	
a (Å)	28.102 (2)
b (Å)	20.5344 (15)
c (Å)	12.7692 (10)
β (deg)	95.7411 (16)
V (Å^3)	7331.6 (9)
Z	4
ρcalcd (g cm^{-3})	1.335
μ (mm^{-1})	0.897

B. Data Collection and Refinement Conditions

diffractometer	Bruker P4/RA/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ϕ rotations (0.3°) / ω scans (0.3°) (30 s exposures)
data collection 2θ limit (deg)	51.50
total data collected	21122 (-34 ≤ h ≤ 33, -24 ≤ k ≤ 25, -15 ≤ l ≤ 15)
independent reflections	12330
number of observations (*NO*)	8806 [$F_o^2 \geq 2\sigma(F_o^2)$]
structure solution method	direct methods/fragment search (DIRDIF–96[c])
refinement method	full-matrix least-squares on F^2 (SHELXL–93[d])
absorption correction method	SADABS
range of transmission factors	0.8620–0.5954
data/restraints/parameters	12330 [$F_o^2 \geq -3\sigma(F_o^2)$] / 3[e] / 663
Flack absolute structure parameter[f]	0.0 (3)
goodness-of-fit (S)[g]	1.005 [$F_o^2 \geq -3\sigma(F_o^2)$]
final R indices[h]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0639
wR_2 [$F_o^2 \geq -3\sigma(F_o^2)$]	0.1993
largest difference peak and hole	1.200 and –0.924 e Å^{-3}

[a]Obtained from least-squares refinement of 5574 centered reflections.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Beurskens, P. T.; Beurskens, G.; Bosman, W. P.; de Gelder, R.; Garcia Granda, S.; Gould, R. O.; Israel, R.; Smits, J. M. M. (1996). The *DIRDIF-96* program system. Crystallography Laboratory, University of Nijmegen, The Netherlands.

[d]Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993. Refinement on F_o^2 for all reflections (all of these having $F_o^2 \geq -3\sigma(F_o^2)$). Weighted R-factors wR_2 and all goodnesses of fit S are based on F_o^2; conventional R-factors R_1 are based on F_o, with F_o set to zero for negative F_o^2. The observed criterion of $F_o^2 > 2\sigma(F_o^2)$ is used only for calculating R_1, and is not relevant to the choice of reflections for refinement. R-factors based on F_o^2 are statistically about twice as large as those based on F_o, and R-factors based on ALL data will be even larger.

[e]An idealized geometry was imposed on one of the solvent dichloromethane molecules: d(Cl(6S)–C(4S) = d(Cl(6S)–C(4S) = 1.80 Å; d(Cl(6S)···Cl(7S) = 2.95 Å.

[f]Flack, H. D. *Acta Crystallogr.* 1983, *A39*, 876–881. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration.

[g]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.1213P)^2]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[h]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

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Chapter 5

Recoverable Catalysts for Asymmetric Hydrogenation: First Example of Reusable ROMPgel Catalyst for Asymmetric Ketone Hydrogenation

Introduction

Transition metal complexes with diphosphine ligands such as BINAP,[1] DUPHOS,[2] and others[3] have proved to be excellent homogeneous catalysts for various asymmetric hydrogenation reactions. The metal-diphosphine complexes for asymmetric hydrogenations and other reactions are expensive and currently there are attempts by several groups to try to "heterogenize" these homogeneous catalysts so they can be easily recycled.[4] Attempts at "heterogenization" have relied mainly on anchoring the homogeneous catalyst to solid inorganic supports[5] or organic supports.[6] In most cases, "heterogenization" has resulted in reduced activity and/or selectivity as compared to the parent catalyst.[7] Hence new strategies for support and recycling of homogeneous catalysts are still being developed.[8]

Most polymeric hydrogenation catalysts on organic supports are made using one of the following types of reactions: radical copolymerization of vinyl derivatives of arenes and phosphines,[9] condensation reactions between acid derivatives and amines or alcohols,[10] condensation polymerizations between diamines and

diisocyanates,[11] Suzuki-type couplings,[12] and halide substitutions using either anionic or amine nucleophiles.[4b] These reactions are used to either polymerize a chiral phosphine ligand, or to graft it to a polymer. The polymeric chiral phosphine is then metallated to produce the catalyst precursor.[9,10,11,12]

To the best of my knowledge, Ring Opening Metathesis Polymerization (ROMP) has not been used to prepare a polymerized asymmetric hydrogenation catalyst.[13] Although ROMP is used extensively to prepare polymer supported reagents (ROMPgels, where "gel" refers to the thickening of the reaction mixtures on stirring) for use in organic synthesis,[14] the number of metal-containing catalysts prepared by ROMP is low. The development of ruthenium-based ROMP catalysts **1** and **2** by Grubbs *et al.*[15] or the molybdenum based catalysts of type **3** by Schrock *et al.*[16] (figure 5-1) has opened up new avenues for the synthesis of polymer

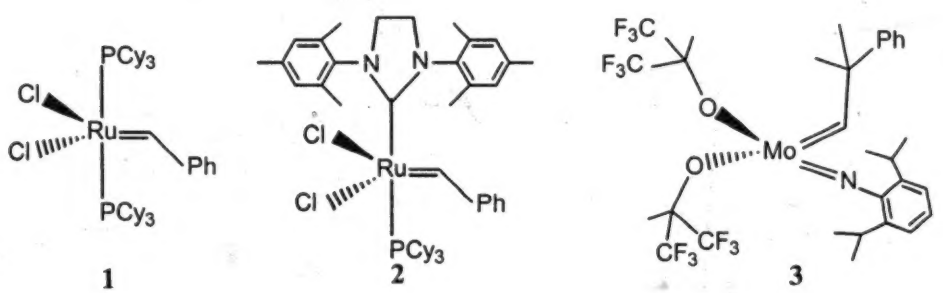
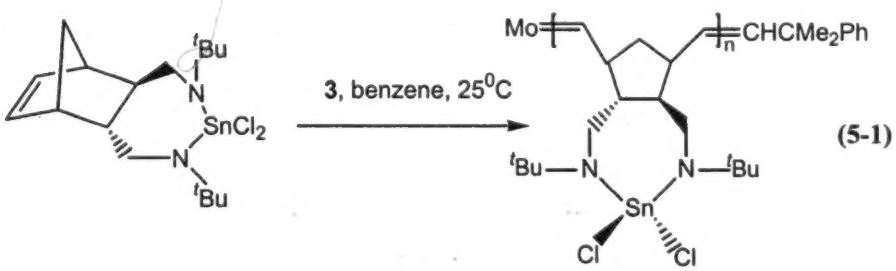


Figure 5-1. Most common ROMP catalysts.

supported reagents. The advantages of these alkylidene complexes over earlier systems, namely stability, high performance, and- most importantly- tolerance

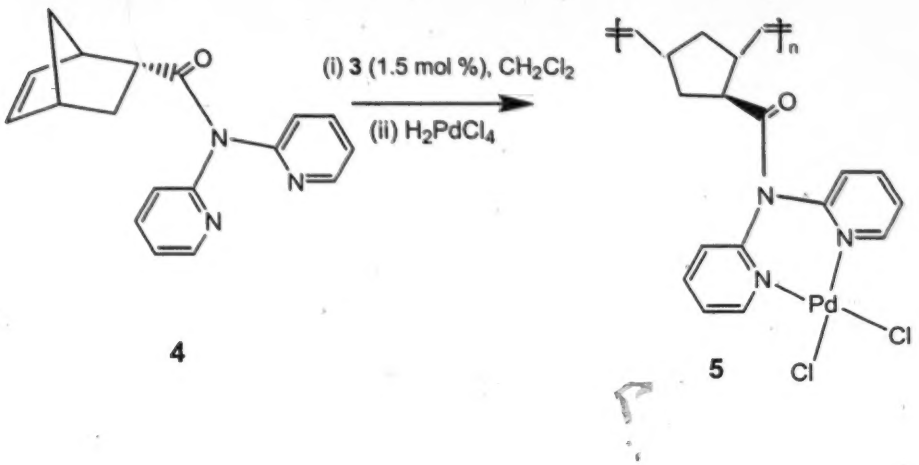
towards a number of functional groups, have made it possible for olefin metathesis to be applied in a wide range of transformations both in organic synthesis[14] and polymer chemistry.[14b,16] The ability of the Mo catalysts to tolerate various functionalities has been utilized by Schrock *et al.*[18] to prepare metal-containing polymers. This is achieved by ROMP of various 2,3-disubstituted norbornenes carrying chelating ligand groups to form polymers that are then reacted with metal containing precursors.[18] Alternatively, metal containing monomers have been polymerized directly to give metal containing polymers (equation 5-1).[19] Most of



(5-1)

these metal-containing polymers prepared by Schrock *et al.* were investigated for their thermal and electrical properties and were not used for any synthetic application. There are, however, a few examples of ROMP polymers containing metals that have been used in catalysis. The first example of such catalysts is the Pd based system used in the Heck C-C coupling reactions.[20] The supported catalyst is prepared via ROMP of monomer **4** using the molybdenum catalyst **3** followed by reaction of the polymer with H_2PdCl_4 to give the catalyst precursor **5** as shown in Scheme 5-1. Polymeric **5** is used as a catalyst precursor for the vinylation of aryl

Scheme 5-1. Synthesis of an immobilized palladium catalyst for Heck reactions



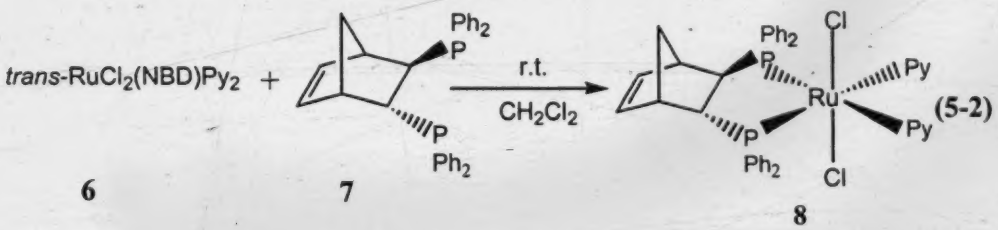
4 5

iodides and aryl bromides and gives very good TON and higher rates relative to the unsupported catalyst. Other examples of metal containing catalysts prepared by ROMP are the Fe based system used for styrene polymerizations,[21] a supported Grubbs' catalyst **1** grafted onto vinyl polystyrene,[22] and Grubbs' catalyst **2**[23a,b] and Schrock's catalyst **3**[23c] grafted onto monolithic supports.

The use of ROMP to support various reagents for different applications is thus well established. We were, therefore, surprised that such a versatile technique has not been utilized for the preparation of polymer supported catalysts in asymmetric hydrogenation, one of the most fundamental transformations in asymmetric catalysis. This chapter will discuss attempts to expand use of ROMPgel methodology to the preparation of supported catalysts for asymmetric hydrogenation. A novel preparation and application of ROMPgel catalysts in asymmetric hydrogenation will be discussed.

Results and Discussion

Monomer for synthesis of ROMPgel catalysts. Transition metal complexes containing the (*R,R*)-NORPHOS ligand (**7**), have been used as catalyst precursors for a variety of asymmetric transformations.[24] Ruthenium-NORPHOS complexes in particular are known to effect asymmetric hydrogenation of prochiral substrates.[25] The discovery of the synthon, *trans*-$RuCl_2(NBD)Py_2$, **6** has made possible the synthesis of ruthenium complexes of type **8** by reaction of **7** with **6** under mild



6 **7** **8**

conditions (equation 5-2). Our interest in compound **8** is based on the premise that, because it contains the strained norbornyl unit and lacks lone pairs that can coordinate to the ROMP catalyst and shut it down, it can be polymerized by ROMP to form ROMPgel supported catalysts. In addition, **8** can easily be converted into the useful ketone hydrogenation catalyst $RuCl_2$(NORPHOS)((*R,R*)-DPEN) by reaction with (*R,R*)-DPEN as was described in Chapter 2. Crystals of **8** suitable for X-ray analysis were obtained by addition of hexanes to a saturated solution of **8** in CH_2Cl_2. The crystal structure is shown in figure 5-2. The relative *cis* disposition of the Py ligands is expected based on related structures given in Chapter 2. The

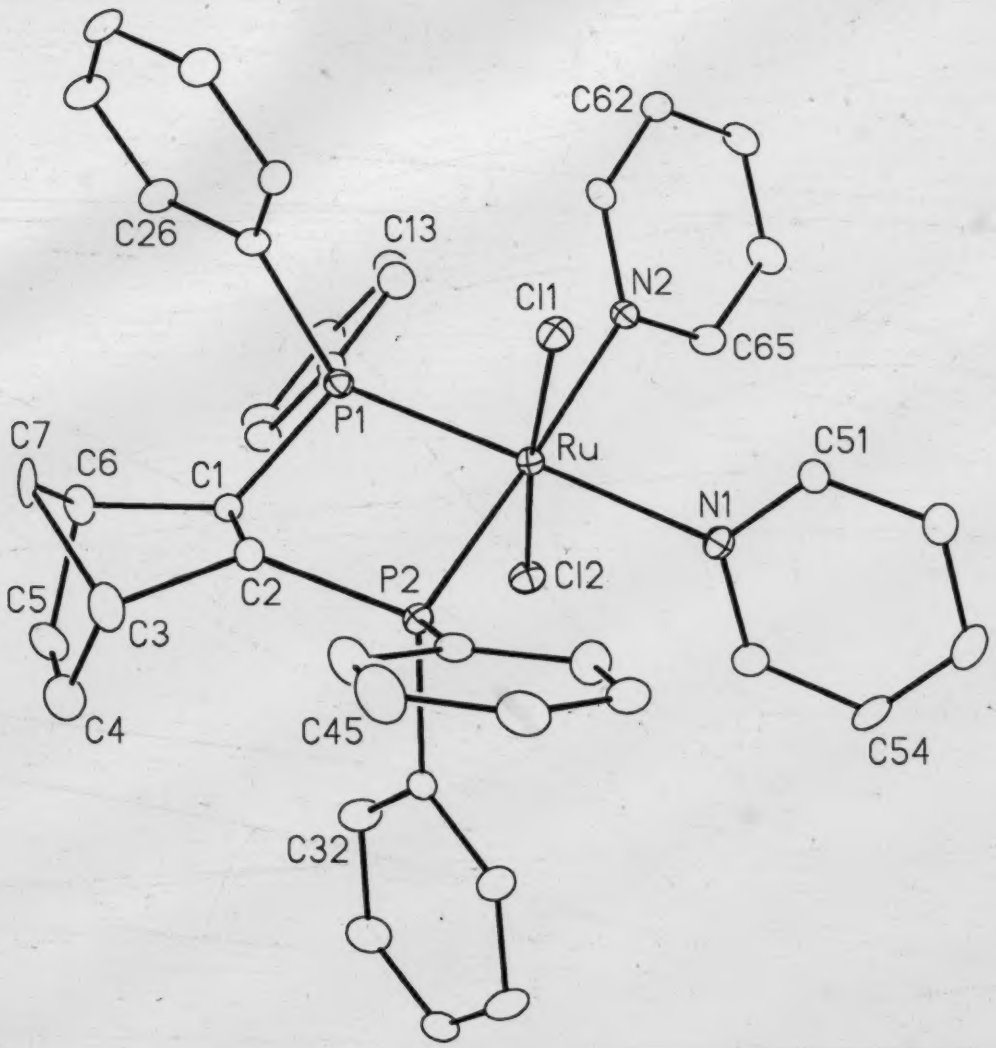


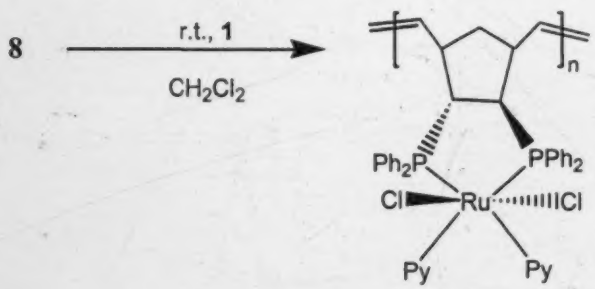
Figure 5-2. Perspective view of **8** showing the atom labeling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at 20 % probability level, hydrogen atoms are omitted.

Table 5-1. Selected Interatomic Distances (Å) and Angles (deg) for 8

Ru–Cl1	2.4249(13)	P2–C2	1.844(5)
Ru–Cl2	2.4102(14)	P2–C31	1.853(5)
Ru–P1	2.3195(15)	P2–C41	1.836(5)
Ru–P2	2.3188(15)	N1–C51	1.349(6)
Ru–N1	2.171(4)	C1–C6	1.573(7)
Ru–N2	2.151(4)	C2–C3	1.584(7)
P1–C1	1.819(5)	C4–C5	1.254(9)
P1–C11	1.838(5)	C11–C12	1.386(7)
P1–C21	1.835(5)	C11–C16	1.382(7)
Cl1–Ru–Cl2	175.00(5)	Ru–P1–C1	103.49(17)
Cl1–Ru–P1	99.17(5)	Ru–P1–C11	115.30(18)
Cl1–Ru–P2	89.36(5)	Ru–P1–C21	127.69(17)
Cl1–Ru–N1	87.55(11)	C1–P1–C11	104.9(2)
Cl1–Ru–N2	87.13(11)	C1–P1–C21	103.3(2)
P1–Ru–P2	87.80(5)	Ru –P2–C2	102.47(17)
P1–Ru–N1	172.92(12)	Ru –P2–C31	120.68(17)
P2–Ru–N2	176.04(12)	Ru–N1–C51	120.8(4)
N1–Ru–N2	87.12(16)	Ru–N2–C65	121.2(3)

diphosphine ligand forms a five-membered ring with λ-conformation that is characteristic of the (*R,R*)-NORPHOS ligand.[26] The metal-ligand distances (Ru-P, Ru-N and Ru-Cl) are all within the range of similar $RuCl_2$(diphosphine)Py_2 complexes that were discussed in Chapters 2 and 3. The bite angle, P1-Ru-P2, of 87.80(5)° is very close to 86.1(1)° that is reported for the only other published Ru(II)-NORPHOS complex.[26] Table 5-1 shows some selected bond lengths and bond angles for **8**.

Initial Attempts to polymerize 8. Attempts were made to polymerize **8** using **1** according to equation 5-3. It was found that when 5 % mol of **1** was added to a golden yellow solution of **8** in CH_2Cl_2 at r.t., the solution changed color to



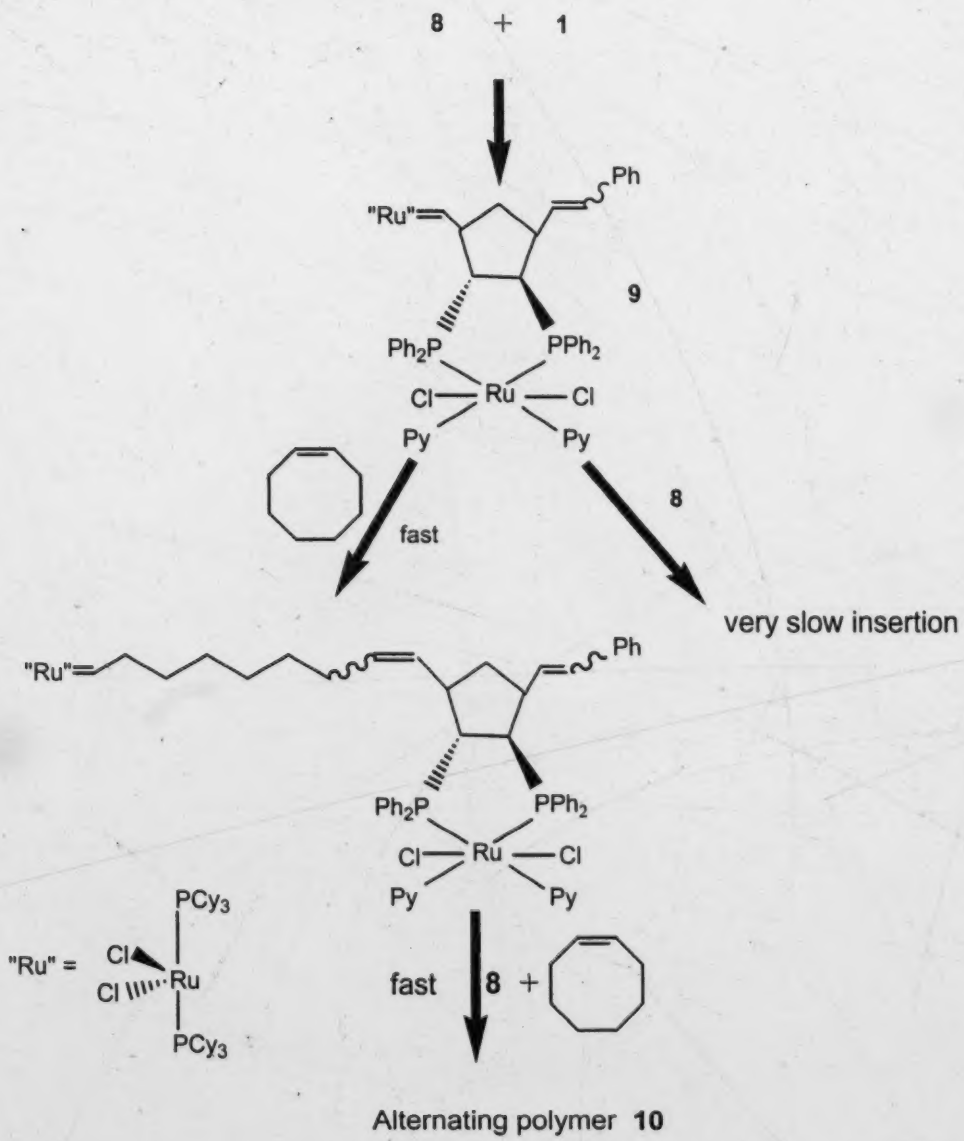
(5-3)

reddish brown. No further color change was observed even after stirring the reaction mixture overnight. A ^{31}P NMR analysis of the product indicated that only traces of the polymer had formed and that most of the starting material remained unreacted. Attempts to force the reaction to go to completion by increasing the reaction

temperature to 50 °C were unsuccessful. A stoichiometric (1:1) reaction between **1** and **8** did not result in rapid polymerization. Instead the reaction was sluggish, requiring 72 h for all of **8** to be consumed. NMR analysis of the reaction mixture after 17 h indicated presence of **1**, **8** and free PCy_3 in addition to minute amounts of polymer. Since the polymerization with **1** was found to be slow, **2**, that is known to give higher rates of polymerizations[27] was tried. Polymerization with the more bulky **2** was found to be even slower than **1**, giving only 33 % conversion after 72 h for a 1:1 reaction with **8**. This result was surprising but seemed to suggest that sterics could be the problem in these polymerizations. Molecular models of the polymer confirmed that units of **8** could not fit side by side in a chain.

It was therefore decided that the polymerization reactions be carried out in the presence of another cyclic olefin that is less strained than **8** and less sterically encumbered. The reasoning was that **8** would react first with Grubbs' catalyst to form the crowded metathesis product **9** (scheme 5-2). We believe this product is sterically constrained and can react only slowly with another molecule of **8**, but can react rapidly with a less sterically encumbered olefin. Cyclooctene (COE) was chosen as the spacer olefin mainly because it satisfies the required conditions and is known to copolymerize with norbornenes in an alternating fashion.[28] The insertion of COE into the "Ru"= C bond of **9** relieves the steric crowding and enables rapid reaction of the sterically encumbered but more reactive **8**. In a trial run, 6 equivalents of COE (relative to **8**) were added to a reaction mixture containing **8** and

Scheme 5-2. Polymerization of 8 and COE using Grubbs catalyst 1



5 % mol of **1** that had been left stirring overnight, almost instantaneously, the mixture started to thicken and within three hours both monomers were completely consumed as determined by ^{31}P NMR spectroscopy. Clearly rapid polymerization of **8** was possible in the presence of a spacer olefin.

Optimization of polymerizations. As shown in Table 5-2, different ratios of COE:**8** were tried in order to establish the right ratio for the polymerization reactions using 5 % mol of **1** in CH_2Cl_2 at r.t. For 1:1 mixtures, polymerization was slow, giving 33 % and 95 % yields after 2 h and 18 h respectively (entry 1). It was found that for rapid polymerizations and good product yield, at least 4 equivalents of COE relative to **8** were required (entry 3). Longer polymers that are insoluble in 2-propanol were required for use in hydrogenation. For such polymers, catalyst loadings of about 1 % mol relative to **8** were found adequate. A typical

Table 5-2. Polymer Yields for Different Ratios of COE:8 Using 5 % mol of 1.

Entry	**8**	COE	Yield / Time
1	1	1	33 % / 2 h; 95 % / 18 h
2	1	2	67 % / 2 h; 100 % / 18 h
3	1	4	77 % / 0.5 h; 100 % / 3.5 h

polymerization reaction was thus carried out with reagent ratios of **1** or **2**:**8**:COE = 1:100:2000, and using 0.1 M solutions of **8** in CH_2Cl_2. Lower loadings of **1** or **2** gave long polymers that precipitated out of solution unless more solvent (5-10 times initial volume) was added. Addition of such quantities of extra solvent had the undesired effect of drastically slowing down the polymerizations and in most cases

resulted in less than 100 % conversions of **8** to product. After set-up, the reaction mixture gradually becomes more viscous indicating that polymers are being formed. In cases where very low catalyst loadings were used, the mixture turned gummy and it was impossible to stir after about 3 h, unless more solvent was added.

Preliminary studies of the polymerization were carried out as variable temperature ^{31}P NMR experiments using a loading ratio **1**:**8**:COE of 1:1:20. The reagents were mixed in a NMR tube at -80 °C and were quickly transferred to the probe. In figure 5-3 (a), the singlet peak at δ = 38.3 is due to **1**[15a,b] and the doublets at approximately δ = 34.0 and 32.5 are due to **8**.[29] As can be seen from the integrations, at –80 °C the ratio of **1**:**8** is 1 (figure 5-3(a)). Upon increasing the temperature, the amount of **8** reduces gradually and at –40 °C, polymer peaks start appearing in the range 50-55 ppm. At 25 °C, **8** is completely consumed and only peaks from **1** and polymer can be seen (figure 5-3 (b)). Integrations of the unreacted catalyst peak at δ = 37.2 and the product catalyst peak at δ = 36.5 show that about 66 % of the ROMP catalyst **1** is incorporated into the polymer. Thus the rate of initiation is slower than the rate of propagation under these conditions.

A ^{31}P NMR analysis of reaction mixtures of long polymers made by mixing reagents in the ratios **1** or **2**:**8**:COE = 1:100:2000 indicated that they consisted of two major species. The first, two doublets (δ = 54.7, J= 34.5Hz; δ = 51.0, J= 34.4 Hz), the second an AB quartet (δ = 52.3) in an approximately 1:1 ratio. On addition of (*R*,*R*)-DPEN to these solutions, the ^{31}P NMR of the polymer changed and now consisted mainly of 5 species centered at δ = 59.10, 60.75, 61.04, 62.39 and 62.62.

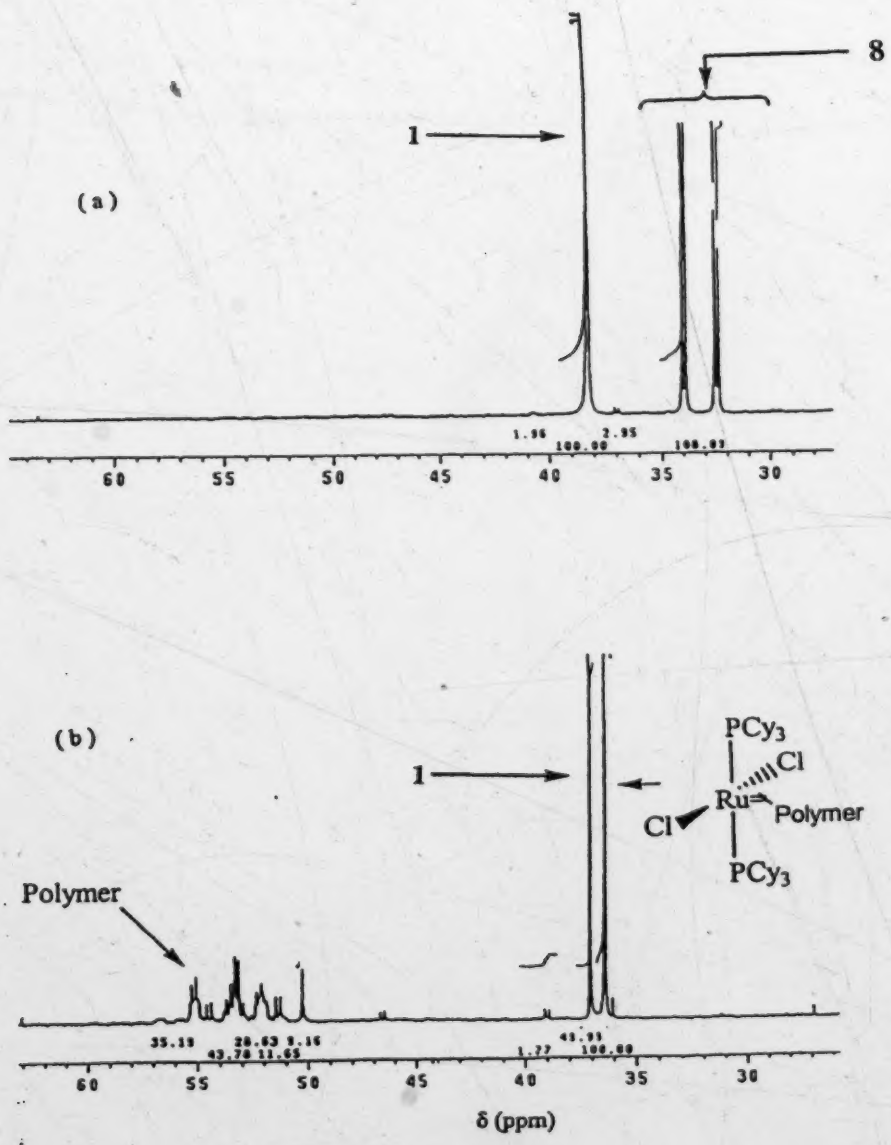


Figure 5-3. Variable temperature $^{31}P\{^{1}H\}$ NMR spectra of a **1**:**8**:COE mixture in the ratio 1:1:20 at (a) –80 °C and (b) 25 °C.

The relative amounts of these species are 40.7 %, 10.2 % 40.7%, 8.0 %, 0.4 % respectively. The chemical shifts and ratios of these peaks remain constant regardless of the polymer length.

The ^{1}H NMR spectra of the polymer also furnishes interesting details. For a polymerization done using 5 % mole of **1** and a COE:**8** ratio of 2:1, it was observed that the proton peaks characteristic of both monomers decreased as broad polymer peaks emerged and increased in size. After 60 % of **8** had reacted, the ratio of COE:**8** in the polymer was less than 1.5:1 indicating a high degree of alternating growth in these polymerizations.

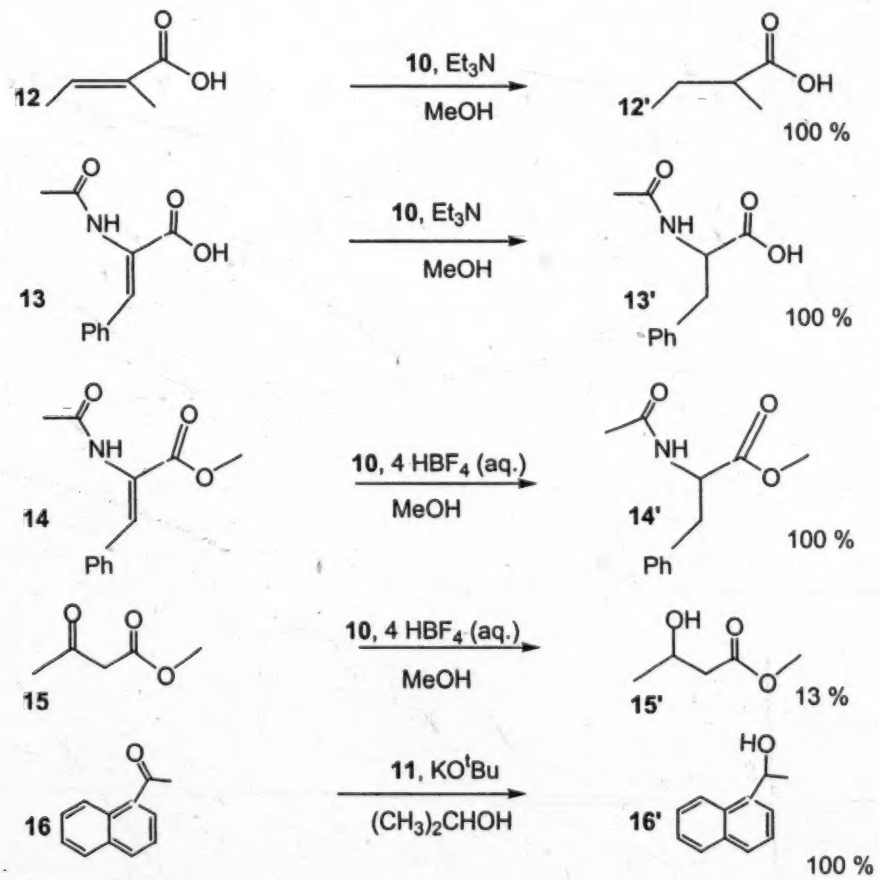
For reasons that are not yet clear, the (*R,R*)-DPEN analogue of **8**, *trans*-$RuCl_2$(NORPHOS)((*R,R*)-DPEN), did not polymerize under similar conditions. This did not, however, present a major problem because solutions of the polymer **10** readily react with an excess of (*R,R*)-DPEN via displacement of Py to form $[RuCl_2(NORPHOS)((R,R)\text{-DPEN})]_n(COE)_m$ (**11**) [where m and n are integers determined by initial ratios of reagents]. After completion of the reaction, the mixtures were diluted by addition of CH_2Cl_2 and then transferred by canula into rapidly stirring solutions of MeOH, where a rubbery product precipitated. This product could not be ground into fine powder even on cooling to –196 °C in liquid N_2. In order to obtain the polymer in fine powder and therefore with a large surface area, other supports onto which the polymer could be deposited were sought.

$BaSO_4$ as polymer support. Support on $BaSO_4$ was achieved by canulating dilute solutions of **10** or **11** onto ultra pure, high reflectance $BaSO_4$. The addition

was done with rapid stirring of the reaction mixture to ensure even distribution of polymer on $BaSO_4$ surface. MeOH was then added to the mixture to precipitate the polymer. The paste obtained after pumping off the solvent can be ground to form a fine powder that was used as a heterogeneous catalyst for asymmetric hydrogenation reactions. To the best of my knowledge this is the first time a polymeric catalyst is dispersed on $BaSO_4$. Previously, ROMP polymers have been supported using monolithic supports,[23a] silica[23d] and polystyrene.[22] In all cases, the support methodology require suitably derivatized solid surfaces onto which the monomers are grafted. In some cases the derivatization process may be a multi-step, time consuming synthesis.[23a]

Sand as polymer support. Attempts were made to use sand as a support for the polymeric catalysts as well. Deposition of the catalyst on sand was done in a similar manner to that described for $BaSO_4$. The sand-supported catalyst, when dry, is free flowing and difficult to distinguish from ordinary sand but for the faint yellow coloration. The sand-supported catalysts were easy to use and product recovery was fast in the early runs. Nonetheless, use of sand support has two main drawbacks. First, large amounts of sand are required in order to obtain a well-distributed and free-flowing sand-supported catalyst (about 1 g of sand for 10 mg of complex). The large amounts of sand needed relatively large volumes of solvent in order for the mixtures to be mechanically stirred and hence the higher concentration limits to which the catalyst could be applied were lowered. Secondly, repeated use resulted in the catalyst peeling off the sand surface and forming a thick viscous layer of

Scheme 5-3. Catalytic hydrogenations using 10 or 11 as catalyst precursors.[a]



[a] All reactions done at 60 °C, 3.7 atm. dihydrogen pressure for 24 hrs using S/C = 100

solution just above the sand. Recovery of product by filtration then becomes a problem with repeated use of catalyst due to this viscous layer.

Hydrogenations. The initial hydrogenation reactions were aimed at finding out whether the polymer was catalytically active. For these trial hydrogenation reactions polymer *rac*-**10** was prepared from **8** made from *rac*-NORPHOS and deposited on $BaSO_4$. The substrates that were hydrogenated at 60 °C, 3.7 atm. H_2 at substrate/catalyst ratio = 100 are shown in Scheme 5-3. Tiglic acid **12**, methyl α-acetoamidocinammic acid (MAA) **13**, and methyl α-acetoamidocinnamate (MAC) **14** were hydrogenated to give 100 % products in 24 h. For methylacetoacetate **15**, the low conversion to product (13 %) is expected since use of the homogeneous catalyst under similar conditions gives about the same yield. Polymer **11** was

Table 5-3. Reuse of 10 for Hydrogenation of 13.

Reusing run[b]	time (h)	% Yield	ee %
1	24	100	65(*R*)
2	24	100	58(*R*)
3	24	100	59(*R*)
4	24	100	60(*R*)
5	24	46	nd[c]

[a] reaction conditions 60 °C, 3.7 atm. dihydrogen gas using MeOH as solvent. [substrate] = 0.45M. catalyst:substrate:Et_3N 1:100:100. [b]Number of times the catalyst is being reused. [c]Not determined.

prepared by reaction of **10** with (*R,R*)-DPEN and used as precursor for hydrogenation of 1'-acetonapthone (**16**) giving 100 % yields in 24 h. After these preliminary studies, attention was shifted to reuse and recovery of these ROMPgel catalysts. For a truly effective polymer-supported catalyst, it is critical that recovery be simple and efficient and that the recovered catalyst retains its activity through multiple cycles.

Chiral polymer **10** was prepared and precipitated as a rubbery solid using MeOH. This rubber-like solid was used as a catalyst precursor for repeat hydrogenations of substrate **13** under conditions shown in scheme 5-3. As can be seen from the results in Table 5-3, the first 4 runs gave 100 % conversions to product (entries 1-4) but loss of activity was evident in subsequent runs. The hydrogenation of **13** with the homogeneous system proceeds with 85 % ee (*R*). The results in Table 5-3 indicate that the use of **10** as catalyst precursor results in lower ee (about 60 %). The relatively large variation in ee values is due to use of shift reagent that is less accurate for ee determination. Due to the large reduction in ee when **10** is used, hydrogenation of **13** was discontinued and other substrates were investigated.

It was thought that in order to maximize the efficiency of the polymeric catalyst, a finer version with larger surface area was required. Polymer **11** was prepared, deposited on $BaSO_4$ and used for repeated hydrogenation of 1'-acetonaphthone (**16** Scheme 5-3) in *iso*-propanol. For repeat runs, a fresh sample of substrate and ^{t}BuOK were introduced into the pressure reactor as a solution in *iso*-

propanol by canula for each run. Under conditions shown in Table 5-4, it was possible to reuse polymer **11** a total of ten times for hydrogenation of **16** and in all

Table 5-4. Hydrogenation of 16 Using 11 Supported on $BaSO_4$[a].

Reusing run[b]	time (h)	% yield	ee %
1	24	100	74(*S*)
2	24	100	74(*S*)
3	24	100	73(*S*)
4	24	100	74(*S*)
5	24	100	nd[d]
6	24	100	nd
7	24	100	nd
8	24	100	nd
9	24	100	nd
10	24	100	nd
11[c]	24	14	nd

[a]reaction conditions: 60 °C, 3.7 atm. dihydrogen using *iso*-propanol as solvent. [Ketone] = 0.18 M; catalyst:base:ketone = 1:5:100. [b]Number of times the catalyst is being used. [c]Done with 1:5000 catalyst:substrate. [d]Not determined.

cases 100 % conversion to product was observed (entries 1-10). The 11th run was carried out at a much higher S/C loading and it was observed that under conditions such as those used for run 11, the polymer dissolves in the substrate.

Having demonstrated reuse of the ROMPgel catalyst **11** for the hydrogenation of **16**, it was of interest to compare its selectivitity and rate to that of the unsupported system. A trial run done to compare the rates of the supported to the unsupported system was carried out using $RuCl_2$(NORPHOS)(*R,R*)-DPEN and **11** under similar conditions. The rate using the heterogeneous catalyst, **11**, was found to be 40 % that

of the homogeneous catalyst indicating a substantial loss of activity upon heterogenization. The selectivity of **11** for the hydrogenation of **16** was however much higher (74 % ee (*S*)) as compared to 51 % ee (*S*) that is obtained using the homogeneous catalyst. This ee value is maintained even when the catalyst is reused 4 times. This is a very interesting result because, in most cases, supported systems give lower activity as well as lower ee when compared to unsupported systems.[30] These findings are however not unprecedented. Chan *et al.*[31] reported that the use of supported BINAP for hydrogenation of 2-(6'-methoxy-2-naphthyl)acrylic acid to produce the anti-inflammatory drug, naproxen, proceeds with a marginally higher selectivity (93 % ee) for the supported system as compared to the unsupported system (89 % ee). Chan's results together with the results reported here do indicate that in certain cases supported systems are more selective. In this particular case, the large increase in ee values when using **11** may be as a result of the structural change in the NORPHOS ligand caused by ROMP, however, further investigation is required to examine this effect as well as possible influences of the support or of polymer conformations on ee values.

Conclusions

The work described in this chapter presents the first example of a ROMP supported catalyst for use in asymmetric hydrogenation. It is also the first time a ruthenium complex containing the NORPHOS ligand has been used as a catalyst for asymmetric hydrogenation of simple aryl-alkyl ketones. It is noteworthy that

catalyst **11** supported on $BaSO_4$ gave higher ee values as compared to the homogeneous system and maintained these values even on repeated use. This is important because loss of selectivity is one of the major problems of supported catalysts. These results do indicate that in certain cases the supported system may be superior to the homogeneous one, hence other methodologies of supporting these catalysts need to be investigated. Moreover, this methodology can be easily adapted to other phosphines simply by attaching a strained olefin to the phosphine and using ROMP to make polymers, thereby avoiding the undesirable functionalization of the polymer backbone. Finally, the demonstrated recyclability of these ROMPgel catalysts may spur interest in the use of ROMP as a methodology for preparation of supported catalysts for asymmetric hydrogenation.

Experimental

Materials and methods. All operations were performed under an argon atmosphere using standard Schlenk techniques. Argon gas (Praxair, 99.998%) was passed through a drying train containing 3 Å molecular sieves and P_4O_{10} before use. Trace quantities of oxygen were removed from H_2 (Praxair, 99.99%) by passage through an Alltech Oxy-Trap. The solvents and reagents, diethyl ether (K, Ph_2CO), *n*-hexane (K, Ph_2CO), methylene chloride (CaH_2), *iso*-propanol ($Mg(O^iPr)_2$), and pyridine (CaH_2) were distilled from drying agents under argon. The diphosphine ligand (*R*,*R*)-NORPHOS was used as received from Strem Chemical Co., Inc. White reflectance $BaSO_4$ was obtained from Eastman Chemical Co., Inc. Unless stated

otherwise, all other reagents were obtained from Aldrich Chemical Co., Inc., of which the liquids were distilled before use. The glass pressure reactor was oven dried and silanized using literature procedures before use.[32] $RuCl_2(NBD)Py_2$, $RuCl_2$ ((*R*,*R*)-NORPHOS)Py_2 and $RuCl_2$((*R*,*R*)-NORPHOS)(*R*,*R*)-DPEN were prepared as described in Chapter 2.

Instrumentation. All ^1H and ^{31}P NMR spectra were measured on a Varian Unity-400 NMR spectrometer operating at 400.15 MHz, and 161.97 MHz respectively. ^1H NMR chemical shifts are reported in parts per million (δ) relative to tetramethylsilane using the solvent as an internal reference. ^{31}P NMR chemical shifts are reported in parts per million (δ) relative to an 85 % H_3PO_4 external reference. All ^{31}P spectra are ^1H decoupled unless stated otherwise. Microanalysis were performed at the University of Alberta Microanalysis Laboratory. Gas chromatography (GC) was performed on a supelco β-Dex 120 column (β-Dex) (30 m x 0.25 mm) fitted to a Hewlett-Packard 5980A gas chromatograph with a Hewlett Packard 3392A integrator.

General procedure for polymerization of a mixture of 8 and COE using 1 or 2 (typical preparation of 10). 0.308 g (0.389 mmol) of **8** were weighed in air and charged into a r.b. flask with a side arm. The flask was then purged with argon gas. In the glove box, 3.2 mg (0.00389 mmol) of **1** were weighed into a sample vial and sealed with a septum. The vial was quickly transferred to the vacuum line and 1.0 mL of freshly distilled CH_2Cl_2 was added to the vial by means of a gas-tight syringe. The catalyst dissolves immediately to form a purple solution. The solution was then transferred by cannula to the flask containing **8**. Instantly **8** dissolved to

give a reddish brown mixture. The vial was further rinsed with 1 mL of CH_2Cl_2 and washings transferred to the reaction flask. Then 0.857 g (1.0 mL, 7.78 mmol) of COE were added by syringe to the reaction mixture. The mixture was stirred at r.t. under inert conditions and after 3 h, the reaction mixture becomes very viscous. Stirring was continued for a further 14 h (total time 17 h) during which time the reaction mixture had turned into a thick viscous brownish-yellow liquid. CH_2Cl_2 (5 mL) was added to the reaction flask and the dilute mixture transferred to a second r.b. flask containing 30 mL of MeOH with rapid stirring. When the polymer solution came into contact with MeOH, a yellow thread-like solid precipitated out of solution. After precipitation, the mixture was stirred for a further 30 min and at this stage the mixture consisted of a yellow suspension in a faintly yellow solvent. The yellow solid was recovered by filtration and washed thrice with MeOH (15 mL) and dried overnight under high vacuum. Elemental analysis. (Calculation assumes 100 molecules of **8** and 2000 molecules of COE were inserted) Calcd for $C_{20143}H_{31872}Cl_{202}N_{200}P_{202}Ru_{101}$: C, 80.51; H, 10.60; N, 0.93. Found: C, 80.08; H, 10.96; N, 0.75. ^{31}P NMR (161.97 MHz, CD_2Cl_2): δ = 48-57 (br m); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 0.8-2.45 (br m, 244 H), 3.0-3.96 (br m, 2H), 4.5-4.8 (m, 2H), 5.0-5.41 (br m, 40H), 6.8-9.0 (m, 30H).

Reaction of 10 with DPEN to form 11. After stirring a 1:100:2000 mixture of **1**:**8**:COE in CH_2Cl_2 at r.t. for 17 h as described above, a solution of (*R,R*)-DPEN 0.248 g (1.17 mmol) in 5 mL of CH_2Cl_2 was added to the flask and the mixture stirred for a further 2 h. The polymer was recovered by filtration after precipitation by addition of MeOH to the reaction mixture. ^{31}P NMR 161.97 MHz, CD_2Cl_2): δ =

53.6-62.7 (br m,); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 0.9-2.5 (br m, 244H), 3.0-5.5 (br m, 8H), 4.5-4.8 (m, 2H), 4.8-5.5 (br m, 40H), 6.8-7.8 (br m, 30H).

Procedure for deposition of 10 or 11 on $BaSO_4$. 10.14 g of high reflectance $BaSO_4$ were weighed in air and charged into 250 mL r.b. flask with a side arm containing a magnetic stirbar. The flask was evacuated and refilled with argon gas three times. Polymer mixture made from a 1:100:2000 of **1**:**8**:COE was diluted by addition of 30 mL of CH_2Cl_2. The polymer mixture was transferred with rapid stirring to the flask containing $BaSO_4$ and formed a thick faint yellow paste. Stirring was stopped and the $BaSO_4$ settled down leaving a yellow supernatant liquid. MeOH (10 mL) were then added to the reaction mixture and the mixture stirred for a further 1 h. Solvents were removed under vacuum to leave a faint yellow paste that was dried under high vacuum for a further 48 h. When dry, this paste could easily be crushed to fine powder by mortar and pestle. In the case of polymer **11**, since the reaction mixture contained excess DPEN, the faint yellow paste was further washed with MeOH (2x30 mL) before being pumped for 48 h on high vacuo.

Procedure for deposition of 10 or 11 on sand. 30.1 g of sand were weighed into a 300 mL beaker and washed with CH_2Cl_2 (3x100 mL). The sand was recovered after each washing by filtration through a Buchner funnel. It was then dried overnight in the oven at 250 °C. The dry sand was removed from the oven, allowed to cool to ambient temperature and transferred to 250 mL r.b. flask. The flask was purged with argon gas by evacuating and refilling three times before the polymer solution of either **10** or **11**, prepared as has been described, was canulated onto the sand with vigorous magnetic stirring, as well as physically shaking the

flask. The solvent was then pumped off the polymer under high vacuum to give wet lumped sand-supported catalyst. The wet sand could be dried further on prolonged pumping (more than 48 h) with very gentle stirring to give free-flowing sand-supported catalyst. This was washed five times with 100 mL of MeOH until no yellow color was observed in the washings. The sand supported polymer was then dried under vacuum for another 48 h.

Variable temperature ^{31}P NMR investigation of a stoichiometric reaction between 1 and 8 in presence of 20 equivalents of COE. Compound **8** (10.5 mg 0.013 mmol) was weighed in air and charged into an NMR tube. The tube was flushed with argon gas for 10 min, sealed with a septum that was firmly held in place by wrapping paraffin film around it. The tube was then immersed in a dry-ice acetone bath at –78 °C. In the glove box, 10.9 mg of **1** (0.013 mmol) were weighed into a sample vial and the vial was sealed with a septum and transferred to the fumehood. CD_2Cl_2 (1.0 mL) was added to the vial to dissolve the catalyst. The resulting purple solution was then transferred slowly, down the walls into the NMR tube containing **8**. Compound **8** dissolved instantly to form a reddish brown solution. Variable temperature ^{31}P NMR were done at –80 °C, -40 °C, O °C and 25 °C and the spectra obtained at -80 °C and 25 °C are shown in figure 5-3.

Purification of substrates. Commercial 1'-acetonaphthone was treated as described in Chapter 3. α-Acetamidocinnamic acid (Aldrich) was recrystallized from EtOH/hexanes mixture as described below: 5.08 g of commercial α-acetamidocinnamic acid were dissolved in minimum amount of anhydrous EtOH(~5 mL) to give an orange solution. A heat gun was used to boil the solution and then

reagent grade hexanes were added to the hot solution until turbidity was observed. The reaction mixture was allowed to cool and stand overnight to form yellowish crystals. This procedure was repeated five times to obtain white crystals of the material.

General procedure for hydrogenation using 10. (typical hydrogenation of **13**). Under an argon atmosphere, the catalyst precursor **10** (48.5 mg), containing 1.31 mg of ruthenium (0.013 mmol), were placed in a glass reactor. The substrate (1.30 mmol), Et_3N (1.30 mmol) and dry, deoxygenated MeOH (2.9 mL) were added to the high pressure glass reactor. The solution was stirred for five minutes before bubbling dihydrogen gas through the solution with rapid stirring for 10 min. The system was then pressurized (40 psi gauge pressure) and vented three times with dihydrogen gas before finally being pressurized to 40 psi. The reactor was placed in an oil-bath at 60 °C and left to react for 24 h. The solutions turned a faint yellow color during hydrogenations. When the reaction was over, the mixture was cooled to ambient temperature, depressurized, and then flushed with dinitrogen before the contents of the reactor were transferred to a flask. The product was recovered by evaporating the solvent on a rotovap. For repeat use of catalyst, the product was obtained from the reactor by filtration using a canula with filter paper. For each run, a fresh sample of substrate and Et_3N were introduced to the reactor as a solution in MeOH under an argon atmosphere via cannula.

General procedure for hydrogenation using 11 supported on $BaSO_4$. Compound **11** (1.00 g) supported on $BaSO_4$, containing 3.93 mg (0.039 mmol) of ruthenium, were weighed in air and charged into a high pressure glass reactor. The

metal screw-on top was tightly attached and the orifice on the metal sealed with a septum. The contents of the bottle were purged with argon gas. *t*-BuOk (21.9 mg, 0.195 mmol) were weighed in the glove box into a sample vial that was then sealed with a septum. *iso*-Propanol (1.0 mL) was added to the vial by syringe to dissolve the base and the so obtained colorless solution was transferred by cannula into the pressure reactor. The argon-saturated substrate (0.664 g, 3.90 mmol) was then transferred to the reactor by canula. Another 21.0 mL of *iso*-propanol were added to the reactor and hydrogen gas bubbled through the mixture for 10 min. The reactor was connected to the dihydrogen source, pressurized and vented thrice before being pressurized to 40 psi and placed in a 60 ^{o}C oil bath. The contents of the reactor were rapidly stirred for 24 h. After completion of the reaction, the product was recovered, for either single use or multiple use of catalyst, as described for **10** above.

Rate comparisons between 11 and the homogeneous system. The setup for the hydrogenation using **11** is as described above. The hydrogenation using the homogeneous catalyst $RuCl_2$((*R*)NORPHOS)((*R,R*)DPEN) was set up as described in chapter 2 for hydrogenation using $RuCl_2$(diphosphine)(DPEN) systems. The reaction was stopped after two h in both cases and the % conversions compared.

Product work-up and determination of absolute configuration and ee. For 1'-acetonaphthone, the work-up and determination of absolute configuration and ee was as described in Chapter 3. For MAA, the product residue was treated by the following procedure: 8.0 mL of 1M HCl were added to flask containing the hydrogenation product and the flask was shaken for 2 min. Reaction mixture was transferred to a 250 mL separatory funnel and product extracted with Et_2O (3x50

mL). The organic extracts were combined and dried over $MgSO_4$ for 2 h. The mixture was filtered and the filtrate pumped down to dryness to yield a white solid, *N*-acetyl-L-phenylalanine. The product was converted to *N*-acetyl-L-phenylalanine methyl ester by esterification with diazomethane[33] and the ee was spectroscopically determined (^{1}H NMR) using the chiral lanthanide shift reagent {tris[3-(hepta-fluoropropyl-hydroxymethylene)-(+)-camphorato]europium(III)acetate}.[34] The ratio of the methoxy signals (1:1 for *rac*-*N*-acetyl-L-phenylalanine methyl ester at 4 ppm) was used to quantify all ee's. In all cases, addition of (*S*)-*N*-acetyl-L-phenylalanine methyl ester caused a decrease in ee indicating that the absolute configuration of the major enantiomer was *R* .

X-ray crystallography. Crystals of **8**•CH_2Cl_2 suitable for structure determination by X-ray were obtained by slow addition of n-hexanes to a saturated solution of **8** in CH_2Cl_2. Data collection, structure solution and structure refinement for **8**•CH_2Cl_2 were performed by Dr. Robert McDonald, Faculty Service Officer, Structure Determination Laboratory, Department of Chemistry, University of Alberta. See Table 5-1 for selected bond lengths and bond angles respectively for **8**•CH_2Cl_2. See table 5-5 for a summary of crystal data, X-ray data collection, structure solution and structure refinement information for **8**•CH_2Cl_2. Final atomic coordinated and displacement parameters may be obtained from X-ray Crystallography Laboratory, Department of Chemistry, University of Alberta with the file code SHB0002.

Table 5-5. Crystallographic Experimental Details for 8•CH_2Cl_2

	A. Crystal Data
formula	$C_{42}H_{40}Cl_4N_2P_2Ru$
formula weight	877.57
crystal dimensions (mm)	0.28 x 0.09 x 0.06
crystal system	orthorhombic
space group	$P2_12_12_1$ (No. 19)
unit cell parameters[a]	
a (Å)	9.5314 (10)
b (Å)	18.082 (2)
c (Å)	22.516 (3)
V (Å^3)	3880.5 (8)
Z	4
ρcalcd (g cm^{-3})	1.502
μ (mm^{-1})	0.796
	B. Data Collection and Refinement Conditions
diffractometer	Bruker P4/RA/SMART 1000 CCD[b]
radiation (λ [Å])	graphite-monochromated Mo Kα (0.71073)
temperature (°C)	–80
scan type	ϕ rotations (0.3°) / σ scans (0.3°) (30 s exposures)
data collection 2θ limit (deg)	53.10
total data collected	19436 (-4 ≤ h ≤ 11, -22 ≤ k ≤ 22, -27 ≤ l ≤ 27)
independent reflections	7956
number of observations (*NO*)	5774 [$F_o^2 \geq 2$ (F_o^2)]
structure solution method	direct methods (*SHELXS–86*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–93*[d])
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.9622–0.8380
data/restraints/parameters	7956 [$F_o^2 \geq -3\sigma(F_o^2)$] / 0 / 470
Flack absolute structure parameter[e]	–0.18 (3)
goodness-of-fit (*S*)[f]	0.931 [$F_o^2 \geq -3\sigma(F_o^2)$]
final R indices[g]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0470
wR_2 [$F_o^2 \geq -3\sigma(F_o^2)$]	0.0928
largest difference peak and hole	0.739 and –0.716 e Å^{-3}

[a]Obtained from least-squares refinement of 8192 centered reflections.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.

[d]Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993. Refinement on F_o^2 for all reflections (all of these having $F_o^2 \geq -3\sigma(F_o^2)$). Weighted *R*-factors wR_2 and all goodnesses of fit *S* are based on F_o^2; conventional *R*-factors R_1 are based on F_o, with F_o set to zero for negative F_o^2. The observed criterion of $F_o^2 > 2\sigma(F_o^2)$ is used only for calculating R_1, and is not relevant to the choice of reflections for refinement. *R*-factors based on F_o^2 are statistically about twice as large as those based on F_o, and *R*-factors based on ALL data will be even larger.

[e]Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0297P)^2]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

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Chapter 6

Conclusions

Synthon for ruthenium(II)-diphosphine catalyst precursors. The ideal synthon for ruthenium(II)-diphosphine catalyst precursors would be one that reacts with a large variety of structurally and electronically diverse diphosphine ligands to give

Any diphosphine + ideal synthon ⟶ catalyst precursor **(6-1)**

well-defined catalyst precursors as shown in equation 6-1. It was discovered during this study that the complex *trans*-$RuCl_2(NBD)Py_2$ (**1**) is one of the more general, if not the most general starting material for synthesis of Ru(II)-diphosphine catalyst precursors. The preparation of **1** via $RuCl_2(NBD)(Pip)_2$ in a two-step reaction has drastically reduced the time required for its preparation from 7 days to under 20 h. This new preparative procedure should make **1** suitable for use even in an industrial setup where economy of time is crucial. All the diphosphines studied, except Me-PennPhos, gave products of the type $RuCl_2(diphosphine)Py_2$ (**2**). For the case of Me-PennPhos the product was $[Ru_2Cl_3(Me\text{-}PennPhos)_2Py_2]^+$ (**3**). The X-ray crystal structure obtained for compound **3** is the first ever for a metal-PennPhos complex.

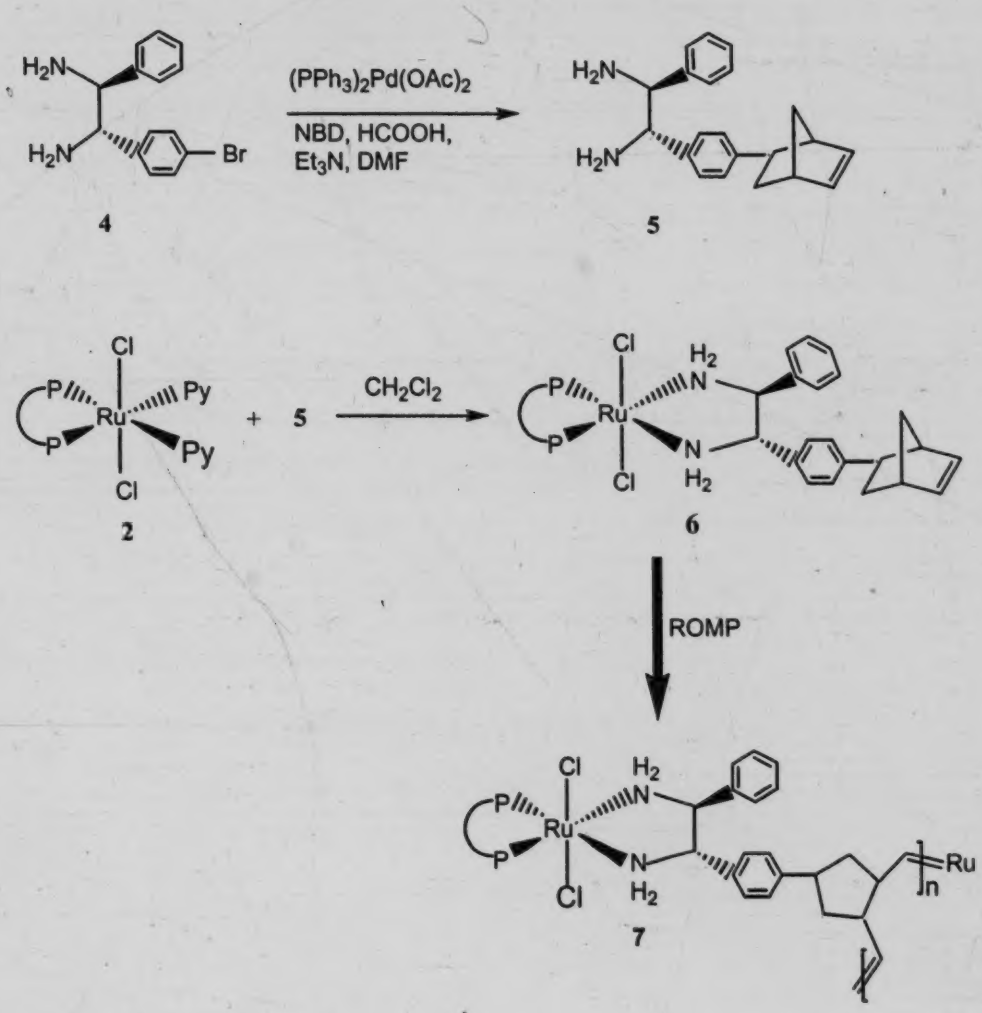
Complexes of type **2** are reported here for the first time as catalyst precursors for asymmetric hydrogenation. A variety of substrates can be hydrogenated using these

complexes; for example α,β- or β,γ-unsaturated acids are hydrogenated in presence of Et_3N, β-ketoesters are hydrogenated in presence of HCl or HBF_4 and aryl-alkyl ketones are hydrogenated in presence of KO^{t}Bu or KOH under mild conditions. The versatility of these complexes is thus unprecedented and makes **1** appropriate for rapid screening of diphosphine ligands on a variety of substrates. Furthermore, the complexes are well-defined and hence convenient to use for mechanistic studies.

The mechanism for hydrogenation of aryl-alkyl ketones using complexes of type **2** is not known at the moment. Future work on these complexes should focus on mechanistic studies. It would be interesting to determine whether or not the catalytic cycle for hydrogenation involve the metal-ligand bifunctional mechanism similar to that displayed by the Noyori systems[1] or whether this is a more classical mechanism involving dissociation of one or both of the Py ligands in order to generate a vacant site for the substrate to coordinate.

Recoverable ROMPgel catalysts for asymmetric hydrogenation. It has been demonstrated, for the first time, in this work that ROMPgel supported metal complexes can be used for asymmetric hydrogenation of a variety of substrates. The reuse of the catalyst can be achieved in cases where a large catalyst surface is exposed. In some cases these catalysts retained their activity for up to 10 runs. Reports of catalyst reuse for more than three runs are rare in literature since most of them tend to loose their activity after the first or second run.[2] The ability of these systems to maintain their activity for a number of runs may well be attributed to the fact that there are a number of

Scheme 6-1. Possible ROMP of a functionalized diamine

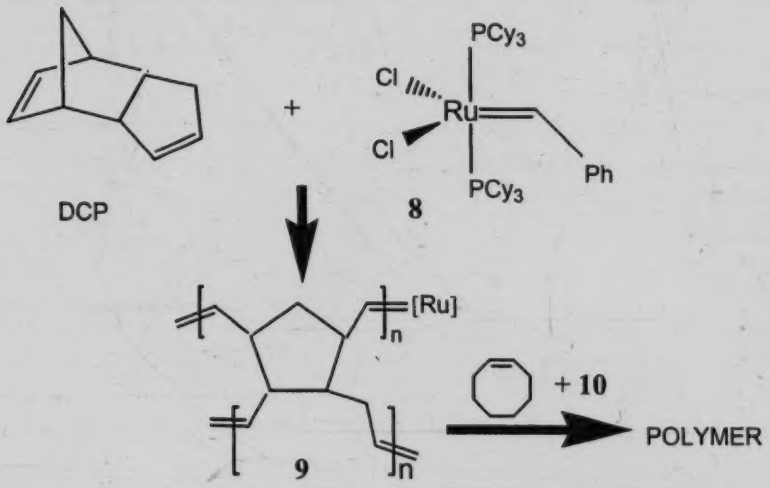


catalyst sites along the polymer chain as opposed to having one site at the end of the chain. Another positive effect was that the polymerized catalyst gave higher ee values in one case when compared to the unpolymerized catalyst. The reasons for this are unclear though it can be suspected that the structural change imposed on the ligand by the ring opening to form a cyclopentane motif could influence the orientation and projection of the phenyl rings on the P atoms of the ligand thus altering the sterics and selectivity of the system.

The ROMP methodology can easily be adapted to any diphosphine or auxiliary ligands such as amines, or any other ligand for that matter. Scheme 6-1 illustrates how a diamine ligand can be derivatized, coordinated to the metal and then ROMP could be used to polymerize the catalyst. The hydroarylation[3] of NBD in presence of derivatized diamine **4** could lead to **5** that does not have other functionalities that could compete with the amino groups for reaction with the metal. To avoid having unattached sites along the polymer chain, **5** is reacted with **2** to generate **6** as was discussed in Chapter 2. Polymerization of **6** should provide an alternative synthetic pathway of producing ROMPgel catalysts **7** in which the norbornene group on the diamine is polymerized as opposed to polymerization of the diphosphine as was the case in this study. Such alternative pathways are currently under investigation in this laboratory.

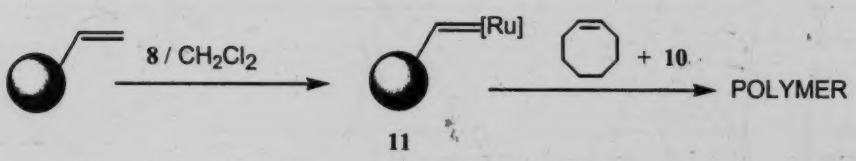
It was observed that very high substrate to catalyst loadings result in polymer dissolution. Perhaps a more cross-linked polymer is required to reduce polymer dissolution. Cross-linking could be achieved by grafting $RuCl_2((R,R)$NORPHOS$)Py_2$ **10** and COE onto a monomer that is capable of cross-linking. Scheme 6-2 shows an example where the "living" nature of ROMP allows grafting of **10** and COE onto a

Scheme 6-2. Grafting polymer onto DCP core



DCP core **9** obtained by polymerization of DCP using catalyst **8**. Other possibilities that can be considered may include use of polymer beads as a support.[4] It is well-known that macroporous resins have a permanent well-developed porous structure even in a dry state. These structure allow rapid swelling of these resins in suitable solvents and in cases where the solvent does not cause the resins to swell, the inner core of the resins may still be accessed due to the presence of these pores.[5] Most importantly, these resins can be treated with toluene solutions of Grubbs' catalyst, for example **8**, to form what is known as ROMP spheres **11** (scheme 6-3).[4(a)] The ROMP spheres can allow grafting of monomer to afford high-loading polymer beads with easily accessible tentacle-like polymer chains.

Scheme 6-3. Grafting of polymer onto macroporous polymer



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The work presented here on ROMP supported catalysts is very preliminary. It is meant to act as a catalyst to spur research into ROMP as a methodology of supporting polymeric catalysts. There is still a lot to be investigated on this methodology and what has been outlined above is only a small part of it. Overall, it has been demonstrated that the ROMP methodology could be used to form ROMPgels that are active as catalyst precursors for asymmetric hydrogenation. In this study polymerization was found to have a positive effect on the selectivity of the supported catalyst. To avoid dissolution of the polymer, known techniques of reducing polymer solubility are under investigation.

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